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L12: Entry 1 of 90 File: USPT Apr 29, 2003

DOCUMENT-IDENTIFIER: US 6555732 B1
TITLE: Rac-like genes and methods of use

Detailed Description Text (51):
Previous studies showed that NIH 3T3 cells stably transformed with a constitutively active isoform of p21Ras (H-Ras .sup.V12), produced large amounts of reactive oxygen species (Irani, et al. Science. 275: 1649-1652). Superoxide dismutase (SOD) quenched the observed signals, whereas catalase had no effect. This result suggested that the observed signals were attributable to 0.0.sub.2 trapping rather than to 0.0H derived from H.sub.2 O.sub.2. Production of 0.0.sub.2 by NIH 3T3 stably transformed with H-Ras.sup.V12 (A6 cells) was confirmed by a Lucigenin-enhanced chemiluminescence (LUCL) assay, which has specificity for 0.0.sub.2 (Gyllenhammar. J. Immunol Methods. 97(2):209-213, 1987) This 0.0.sub.2 production was suppressed by the expression of dominant negative isoforms of Ras or Rac1 as well as by treatment with farnesyl protein transferase (FPTase), which inhibits Ras-dependent transformation and results in morphological reversion of Ras-transformed cells (Kohl, et al. Science 260:1934-1937 (1993), This observation showed that 0.0.sub.2 in A6 cells is dependent on oncogenic Ras. The results also showed, Ras-transformed cells have the ability to progress through the cell cycle even under conditions of confluence and growth factors deprivation and these cells displayed a greater rate of DNA synthesis than the controls (Irani, supra). Treating cells with the antioxidant N-acetyl-L-cysteine (NAC) which inhibits DNA synthesis inhibited the Ras-induced mitogenic response of A6 cells. Furthermore, the mitogenic-activated protein kinase (MAPK) activity was decreased and c-Jun N-terminal kinase (JNK) was not activated in H-Ras-transformed cells. In conclusion, these results indicate that H-Ras.sup.V12 -induced transformation can lead to the production of 0.0.sub.2 through one or more pathways involving Rac1. The implication of a reactive oxygen species, probably 0.0.sub.2, as a mediator of Ras-induced cell cycle progression independent of MAPK and JNK (perhaps JAK/STAT pathway) suggests a possible mechanism for the effects of antioxidants against Ras-induced cellular transformation.

# WEST

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**Search Results** - Record(s) 1 through 10 of 90 returned.

☐ 1. Document ID: US 6555732 B1

L12: Entry 1 of 90 File: USPT Apr 29, 2003

US-PAT-NO: 6555732
DOCUMENT-IDENTIFIER: US 6555732 B1

TITLE: Rac-like genes and methods of use

DATE-ISSUED: April 29, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Duvick; Jonathan P. | Des Moines | IA | | |
| Sharma; Yogesh Kumar | Maryland Heights | MO | | |

US-CL-CURRENT: 800/279; 435/252.3, 435/254.2, 435/320.1, 435/325, 435/419, 435/468, 435/69.1, 536/23.2, 536/23.6, 536/24.1, 536/24.5, 800/278, 800/286, 800/295, 800/298, 800/320, 800/320.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6548734 B1

L12: Entry 2 of 90 File: USPT Apr 15, 2003

US-PAT-NO: 6548734
DOCUMENT-IDENTIFIER: US 6548734 B1

TITLE: Methods relating to modulation of cartilage cell growth and/or differentiation by modulation of NFATp activity

DATE-ISSUED: April 15, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Glimcher; Laurie H. | West Newton | MA | | |
| Ranger; Ann M. | Brighton | MA | | |

US-CL-CURRENT: 800/3; 424/9.1, 424/9.2, 435/4, 435/6, 800/13, 800/14, 800/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 6548650 B1

L12: Entry 3 of 90 File: USPT Apr 15, 2003

US-PAT-NO: 6548650
DOCUMENT-IDENTIFIER: US 6548650 B1

TITLE: Nucleic acid encoding melanoma differentiation associated gene-9

DATE-ISSUED: April 15, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Fisher; Paul B. | Scarsdale | NY | | |

US-CL-CURRENT: 536/22.1; 435/6, 435/7.2, 435/7.23, 436/63, 436/64, 530/300

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 4. Document ID: US 6548540 B2

L12: Entry 4 of 90 File: USPT Apr 15, 2003

US-PAT-NO: 6548540
DOCUMENT-IDENTIFIER: US 6548540 B2

TITLE: Method of treating cancer using dithiocarbamate derivatives

DATE-ISSUED: April 15, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Kennedy; Thomas Preston | Charlotte | NC | | |

US-CL-CURRENT: 514/479; 514/476, 514/478, 514/483, 514/491, 514/499, 514/825, 514/826, 514/922

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 5. Document ID: US 6541046 B2

L12: Entry 5 of 90 File: USPT Apr 1, 2003

US-PAT-NO: 6541046
DOCUMENT-IDENTIFIER: US 6541046 B2

TITLE: Herbal composition and method for controlling body weight and composition

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Wei; Kaiyuan | late of Beijing | | | CN |
| Xu; Xiurong | Dormitory of Beijing Normal University, Beijing | | | CN |

US-CL-CURRENT: 424/756; 424/725, 424/746, 424/773

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 6. Document ID: US 6514745 B1

L12: Entry 6 of 90 File: USPT Feb 4, 2003

US-PAT-NO: 6514745
DOCUMENT-IDENTIFIER: US 6514745 B1

TITLE: Oncoprotein protein kinase

DATE-ISSUED: February 4, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Karin; Michael | San Diego | CA | | |
| Hibi; Masahiko | San Diego | CA | | |
| Lin; Anning | La Jolla | CA | | |
| Davis; Roger | Princeton | MA | | |
| Derijard; Benoit | Shrewsbury | MA | | |

US-CL-CURRENT: 435/252.3; 435/320.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 7. Document ID: US 6511800 B1

L12: Entry 7 of 90 File: USPT Jan 28, 2003

US-PAT-NO: 6511800
DOCUMENT-IDENTIFIER: US 6511800 B1

TITLE: Methods of treating nitric oxide and cytokine mediated disorders

DATE-ISSUED: January 28, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Singh; Inderjit | Mount Pleasant | SC | | |

US-CL-CURRENT: 435/4; 435/26

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 8. Document ID: US 6492332 B1

L12: Entry 8 of 90 File: USPT Dec 10, 2002

US-PAT-NO: 6492332
DOCUMENT-IDENTIFIER: US 6492332 B1

TITLE: Irrigation solution and methods for inhibition of tumor cell adhesion, pain and inflammation

DATE-ISSUED: December 10, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Demopulos; Gregory A. | Mercer Island | WA | | |
| Pierce-Palmer; Pamela | San Francisco | CA | | |
| Herz; Jeffrey M. | Mill Creek | WA | | |
| Tanelian; Darrell L. | Dallas | TX | | |

US-CL-CURRENT: 514/12; 514/217, 514/226.2, 514/25, 514/254.06, 514/259.1, 514/263.1, 514/266.1, 514/280, 514/288, 514/317, 514/327, 514/353, 514/356, 514/397, 514/413, 514/415, 514/509, 514/619, 514/654, 514/680

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 9. Document ID: US 6475986 B1

L12: Entry 9 of 90 File: USPT Nov 5, 2002

US-PAT-NO: 6475986
DOCUMENT-IDENTIFIER: US 6475986 B1

TITLE: Uses of THANK, a TNF homologue that activates apoptosis

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Aggarwal; Bharat B. | Houston | TX | | |

US-CL-CURRENT: 514/12; 424/9.1, 436/64, 436/86, 514/1, 514/2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 10. Document ID: US 6472520 B2

L12: Entry 10 of 90 File: USPT Oct 29, 2002

US-PAT-NO: 6472520
DOCUMENT-IDENTIFIER: US 6472520 B2

TITLE: Rat PEG-3 promoter

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Fisher; Paul B. | Scarsdale | NY | | |

US-CL-CURRENT: 536/24.1; 435/320.1, 536/23.1



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| c-jun same inhibit | 90 |

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L12: Entry 14 of 90 File: USPT Aug 27, 2002

DOCUMENT-IDENTIFIER: US 6441053 B1
TITLE: Inhibitors of glycogen synthase kinase-3 and methods for identifying and using the same

Detailed Description Text (113):
The transcription factor, c-Jun, has been demonstrated to be a substrate for GSK-3 both in vitro and in cell lines overexpressing GSK-3 and c-Jun. GSK-3 phosphorylates c-Jun at three amino acids, specifically Thr-239, Ser-243, and Ser-249 near the DNA binding domain of c-Jun. Phosphorylation of c-Jun at these amino acid positions inhibits DNA binding which, in turn, inhibits c-Jun activity (Boyle et al., 1991, Cell 64:573-584; Plyte et al., 1992, Biochim. Biophys. Acta 1114:147-162). In order to determine whether lithium induces activation of endogenous c-Jun by inhibiting GSK-3 in Xenopus embryos, the following experiments were performed.

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**Search Results** - Record(s) 11 through 20 of 90 returned.

☐ 11. Document ID: US 6472516 B1

L12: Entry 11 of 90 File: USPT Oct 29, 2002

US-PAT-NO: 6472516
DOCUMENT-IDENTIFIER: US 6472516 B1

TITLE: Progestin-regulated gene

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Watts; Colin Kenneth William | Avalon | | | AU |
| Hamilton; Jenny Ann | London | | | GB |

US-CL-CURRENT: 536/23.5; 435/15, 435/183, 435/194, 435/21, 435/69.1, 530/350, 536/24.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 12. Document ID: US 6465618 B1

L12: Entry 12 of 90 File: USPT Oct 15, 2002

US-PAT-NO: 6465618
DOCUMENT-IDENTIFIER: US 6465618 B1

TITLE: Mitogen activated protein kinase (MAPK) kinase

DATE-ISSUED: October 15, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Nishida; Eisuke | Kyoto | | | JP |
| Moriguchi; Tetsuo | Kyoto | | | JP |
| Matsuzaki; Osamu | Fuji | | | JP |

US-CL-CURRENT: 530/350; 435/194, 435/252.3, 435/254.11, 435/320.1, 435/325, 435/471, 435/69.1, 435/71.1, 435/71.2, 536/23.2, 536/24.3, 536/24.31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 13. Document ID: US 6451546 B1

L12: Entry 13 of 90 File: USPT Sep 17, 2002

US-PAT-NO: 6451546
DOCUMENT-IDENTIFIER: US 6451546 B1

TITLE: Plant glutamate receptors

DATE-ISSUED: September 17, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Coruzzi; Gloria | New York | NY | | |
| Oliveira; Igor | New York | NY | | |
| Lam; Hon-Ming | New York | NY | | |
| Hsieh; Ming-Hsiun | Woodside | NY | | |

US-CL-CURRENT: 435/7.2; 435/69.1, 435/7.1, 436/501

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 14. Document ID: US 6441053 B1

L12: Entry 14 of 90 File: USPT Aug 27, 2002

US-PAT-NO: 6441053
DOCUMENT-IDENTIFIER: US 6441053 B1

TITLE: Inhibitors of glycogen synthase kinase-3 and methods for identifying and using the same

DATE-ISSUED: August 27, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Klein; Peter S. | Wynnewood | PA | | |
| Melton; Douglas | Lexington | MA | | |

US-CL-CURRENT: 514/789; 424/610, 435/15, 514/183, 514/211.01, 514/410

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 15. Document ID: US 6433011 B1

L12: Entry 15 of 90 File: USPT Aug 13, 2002

US-PAT-NO: 6433011
DOCUMENT-IDENTIFIER: US 6433011 B1

TITLE: Method for inhibiting formation of aberrant crypt foci in the colon of a mammal

DATE-ISSUED: August 13, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Chung; Fung-Lung | Yorktown Hts. | NY | | |
| Reddy; Bandaru | Suffern | NY | | |
| Conaway; C. Clifford | Mahopac | NY | | |

US-CL-CURRENT: 514/514; 514/741

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 16. Document ID: US 6410713 B1

L12: Entry 16 of 90 File: USPT Jun 25, 2002

US-PAT-NO: 6410713
DOCUMENT-IDENTIFIER: US 6410713 B1

TITLE: DNA encoding proteins that inhibit Hsp70 function

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Guerriero; Vincent | Tucson | AZ | 85718 | |
| Raynes; Deborah A. | Tucson | AZ | 85704 | |

US-CL-CURRENT: 536/23.5; 435/69.1, 435/70.1, 435/91.1, 530/350, 530/412, 530/417, 530/418, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 17. Document ID: US 6410693 B1

L12: Entry 17 of 90 File: USPT Jun 25, 2002

US-PAT-NO: 6410693
DOCUMENT-IDENTIFIER: US 6410693 B1

TITLE: Inhibitors of the JNK signal transduction pathway and methods of use

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Davis; Roger J. | Princeton | MA | 01541 | |
| Dickens; Martin | Bristol B53 1AT | | | GB |

US-CL-CURRENT: 530/388.26; 530/325, 530/326, 530/327, 530/328, 530/329, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 18. Document ID: US 6410323 B1

L12: Entry 18 of 90 File: USPT Jun 25, 2002

US-PAT-NO: 6410323
DOCUMENT-IDENTIFIER: US 6410323 B1

TITLE: Antisense modulation of human Rho family gene expression

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Roberts; M. Luisa | Noank | CT | | |
| Cowsert; Lex M. | Carlsbad | CA | | |

US-CL-CURRENT: 435/375; 435/325, 435/366, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 19. Document ID: US 6399297 B1

L12: Entry 19 of 90 File: USPT Jun 4, 2002

US-PAT-NO: 6399297
DOCUMENT-IDENTIFIER: US 6399297 B1

TITLE: Antisense modulation of expression of tumor necrosis factor receptor-associated factors (TRAFs)

DATE-ISSUED: June 4, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Baker; Brenda F. | Carlsbad | CA | | |
| Cowsert; Lex M. | Carlsbad | CA | | |
| Monia; Brett P. | La Costa | CA | | |
| Xu; Xaoxing S. | Maddison | NJ | | |

US-CL-CURRENT: 435/6; 435/375, 435/91.1, 536/23.1, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 20. Document ID: US 6372753 B1

L12: Entry 20 of 90 File: USPT Apr 16, 2002

US-PAT-NO: 6372753
DOCUMENT-IDENTIFIER: US 6372753 B1

TITLE: Method of preventing proliferation of retinal pigment epithelium by retinoic acid receptor agonists

DATE-ISSUED: April 16, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Campochiaro; Peter A. | Baltimore | MD | | |
| Wheeler; Larry A. | Irvine | CA | | |
| Chandraratna; Roshantha A. | Laguna Hills | CA | | |
| Nagpal; Sunil | Lake Forest | CA | | |
| De Juan, Jr.; Eugene | Phoenix | MD | | |

US-CL-CURRENT: 514/277; 514/725, 514/912



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| Terms | Documents |
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| c-jun same inhibit | 90 |

**Display Format:** CIT | Change Format

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**Search Results** - Record(s) 21 through 30 of 90 returned.

☐ 21. Document ID: US 6361968 B1

L12: Entry 21 of 90 File: USPT Mar 26, 2002

US-PAT-NO: 6361968
DOCUMENT-IDENTIFIER: US 6361968 B1

TITLE: Extension of a protein-protein interaction surface to inactive the function of a cellular protein

DATE-ISSUED: March 26, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Vinson; Charles R. | Silver Spring | MD | | |
| Krylov; Dmitry | Rockville | MD | | |

US-CL-CURRENT: 435/69.1; 530/300, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 22. Document ID: US 6342595 B1

L12: Entry 22 of 90 File: USPT Jan 29, 2002

US-PAT-NO: 6342595
DOCUMENT-IDENTIFIER: US 6342595 B1

TITLE: Oncoprotein protein kinase

DATE-ISSUED: January 29, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Karin; Michael | San Diego | CA | | |
| Hibi; Masahiko | San Diego | CA | | |
| Lin; Anning | La Jolla | CA | | |

US-CL-CURRENT: 536/23.5; 435/252.3, 435/320.1, 435/69.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 23. Document ID: US 6333170 B1

L12: Entry 23 of 90 File: USPT Dec 25, 2001

US-PAT-NO: 6333170
DOCUMENT-IDENTIFIER: US 6333170 B1

TITLE: Method and product for regulating cell responsiveness to external signals

DATE-ISSUED: December 25, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Johnson; Gary L. | Boulder | CO | | |

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 536/23.1, 536/24.31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

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☐ 24. Document ID: US 6313310 B1

L12: Entry 24 of 90 File: USPT Nov 6, 2001

US-PAT-NO: 6313310
DOCUMENT-IDENTIFIER: US 6313310 B1
**** See image for Certificate of Correction ****

TITLE: 4-and 5-alkynyloxindoles and 4-and 5-alkenyloxindoles

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Luk; Kin-Chun | North Caldwell | NJ | | |
| Mahaney; Paige E. | Montclair | NJ | | |
| Mischke; Steven Gregory | Florham Park | NJ | | |

US-CL-CURRENT: 548/312.1; 548/110, 548/486

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

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☐ 25. Document ID: US 6312900 B1

L12: Entry 25 of 90 File: USPT Nov 6, 2001

US-PAT-NO: 6312900
DOCUMENT-IDENTIFIER: US 6312900 B1

TITLE: Antisense oligonucleotide compositions and methods for the modulation of activating protein 1

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Dean; Nicholas M. | Encinitas | CA | | |
| McKay; Robert | San Diego | CA | | |
| Miraglia; Loren | Encinitas | CA | | |
| Baker; Brenda | Carlsbad | CA | | |

US-CL-CURRENT: 435/6; 435/325, 435/375, 435/91.1, 514/44, 536/23.1, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 26. Document ID: US 6307056 B1

L12: Entry 26 of 90 File: USPT Oct 23, 2001

US-PAT-NO: 6307056
DOCUMENT-IDENTIFIER: US 6307056 B1

TITLE: 4-aryloxindoles

DATE-ISSUED: October 23, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Corbett; Wendy Lea | Randolph | NJ | | |
| Luk; Kin-Chun | North Caldwell | NJ | | |
| Mahaney; Paige E. | Montclair | NJ | | |

US-CL-CURRENT: 548/312.1; 548/455, 548/466, 548/468, 548/486

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

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☐ 27. Document ID: US 6294350 B1

L12: Entry 27 of 90 File: USPT Sep 25, 2001

US-PAT-NO: 6294350
DOCUMENT-IDENTIFIER: US 6294350 B1

TITLE: Methods for treating fibroproliferative diseases

DATE-ISSUED: September 25, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Peterson; Theresa C. | Nova Scotia | | | CA |

US-CL-CURRENT: 435/29; 424/277.1, 424/551, 424/553, 424/9.1, 435/17, 435/4, 435/975

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 28. Document ID: US 6288089 B1

L12: Entry 28 of 90 File: USPT Sep 11, 2001

US-PAT-NO: 6288089
DOCUMENT-IDENTIFIER: US 6288089 B1

TITLE: Use of kinase inhibitors for treating neurodegenerative diseases

DATE-ISSUED: September 11, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Zawada; Michael | Denver | CO | 80231 | |
| Heidenreich; Kim | Denver | CO | 80220 | |
| Freed; Curt | Denver | CO | 80231 | |

US-CL-CURRENT: 514/341; 514/275

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 29. Document ID: US 6221867 B1

L12: Entry 29 of 90 File: USPT Apr 24, 2001

US-PAT-NO: 6221867
DOCUMENT-IDENTIFIER: US 6221867 B1
**** See image for Certificate of Correction ****

TITLE: 4,5-pyrazinoxindoles

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Luk; Kin-Chun | North Caldwell | NJ | | |
| Michoud; Christophe | New York | NY | | |

US-CL-CURRENT: 514/250; 544/343, 544/345

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 30. Document ID: US 6221850 B1

L12: Entry 30 of 90 File: USPT Apr 24, 2001

US-PAT-NO: 6221850

DOCUMENT-IDENTIFIER: US 6221850 B1

TITLE: Antisense oligonucleotide compositions and methods for the modulation of JNK proteins

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| McKay; Robert | La Mesa | CA | | |
| Dean; Nicholas | Olivenhain | CA | | |
| Monia; Brett P. | La Costa | CA | | |
| Nero; Pamela Scott | Oceanside | CA | | |
| Gaarde; William A. | Carlsbad | CA | | |

US-CL-CURRENT: 514/44; 435/183, 435/194, 435/320.1, 435/325, 435/371, 435/91.1, 536/23.1, 536/24.31, 536/24.5



| Terms | Documents |
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| c-jun same inhibit | 90 |

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
 NEWS  3  Jun 03  New e-mail delivery for search results now available
 NEWS  4  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS  5  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS  6  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS  7  Sep 03  JAPIO has been reloaded and enhanced
 NEWS  8  Sep 16  Experimental properties added to the REGISTRY file
 NEWS  9  Sep 16  CA Section Thesaurus available in CAPLUS and CA
 NEWS 10  Oct 01  CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 11  Oct 24  BEILSTEIN adds new search fields
 NEWS 12  Oct 24  Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 13  Nov 18  DKILIT has been renamed APOLLIT
 NEWS 14  Nov 25  More calculated properties added to REGISTRY
 NEWS 15  Dec 04  CSA files on STN
 NEWS 16  Dec 17  PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 17  Dec 17  TOXCENTER enhanced with additional content
 NEWS 18  Dec 17  Adis Clinical Trials Insight now available on STN
 NEWS 19  Jan 29  Simultaneous left and right truncation added to COMPENDEX,
                  ENERGY, INSPEC
 NEWS 20  Feb 13  CANCERLIT is no longer being updated
 NEWS 21  Feb 24  METADEX enhancements
 NEWS 22  Feb 24  PCTGEN now available on STN
 NEWS 23  Feb 24  TEMA now available on STN
 NEWS 24  Feb 26  NTIS now allows simultaneous left and right truncation
 NEWS 25  Feb 26  PCTFULL now contains images
 NEWS 26  Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results
 NEWS 27  Mar 19  APOLLIT offering free connect time in April 2003
 NEWS 28  Mar 20  EVENTLINE will be removed from STN
 NEWS 29  Mar 24  PATDPAFULL now available on STN
 NEWS 30  Mar 24  Additional information for trade-named substances without
                  structures available in REGISTRY
 NEWS 31  Apr 11  Display formats in DGENE enhanced
 NEWS 32  Apr 14  MEDLINE Reload
 NEWS 33  Apr 17  Polymer searching in REGISTRY enhanced
 NEWS 34  Apr 21  Indexing from 1947 to 1956 being added to records in CA/CAPLUS
 NEWS 35  Apr 21  New current-awareness alert (SDI) frequency in
                  WPIDS/WPINDEX/WPIX
 NEWS 36  Apr 28  RDISCLOSURE now available on STN
 NEWS 37  May 05  Pharmacokinetic information and systematic chemical names
                  added to PHAR

 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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=> file medline, dgene, embase, wpids, biosis, biobusiness, jicst, fsta
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FULL ESTIMATED COST                                 0.42       0.42

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=> s c-jun
L1       27419 C-JUN

=> s janus kinase
L2        4397 JANUS KINASE

=> s jak-3
L3         248 JAK-3

=> s ara-C
L4       11165 ARA-C

=> s topoisomerase II inhibitor
L5        1457 TOPOISOMERASE II INHIBITOR

=> s l1 and activation
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L6 14563 L1 AND ACTIVATION

=> s l2 and l3
L7 91 L2 AND L3

=> s l7 and inhibit?
L8 49 L7 AND INHIBIT?

=> s l4 and l6
L9 40 L4 AND L6

=> s l9 and l5
L10 0 L9 AND L5

=> s l5 and l6
L11 4 L5 AND L6

=> d l11 ti abs ibib tot

L11 ANSWER 1 OF 4 MEDLINE
TI **Activation** of the tumor metastasis suppressor gene, KAI1, by etoposide is mediated by p53 and **c-Jun** genes.
AB KAI1 is a metastasis suppressor gene which is capable of inhibiting the processes of tumor metastasis without affecting tumorigenicity per se. We found that etoposide, a **topoisomerase II inhibitor**, is able to activate the expression of the KAI1 gene in a dose-dependent manner in human prostate cancer cell lines, ALVA, DU145, and PC-3 as well as in human lung carcinoma cell A549. The **activation** of the KAI1 gene was mainly mediated by the **c-Jun** gene in the PC-3 and DU145 cell lines, while it was mediated by both p53 and **c-Jun** genes in the A549 cell line. These results suggest that the augmentation of the KAI1 gene expression is independently controlled by p53 and **c-Jun** at the transcriptional level in the human cancer cell lines. Furthermore, treatment of these cell lines with etoposide resulted in significant reduction of cellular invasion measured by the Matrigel invasion chamber. Because etoposide has been shown to be effective on advanced prostate cancer when used in combination with other regimens, our results provide further rationale to use this drug as an antimetastatic agent.

ACCESSION NUMBER: 2000408778 MEDLINE
DOCUMENT NUMBER: 20374474 PubMed ID: 10913345
TITLE: **Activation** of the tumor metastasis suppressor gene, KAI1, by etoposide is mediated by p53 and **c-Jun** genes.
AUTHOR: Mashimo T; Bandyopadhyay S; Goodarzi G; Watabe M; Pai S K; Gross S C; Watabe K
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, Southern Illinois University School of Medicine, Springfield, Illinois, 62702, USA.
CONTRACT NUMBER: R15 CA67290 01 (NCI)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Aug 2) 274 (2) 370-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000824

L11 ANSWER 2 OF 4 EMBASE 

TI **Activation** of the tumor metastasis suppressor gene, KAI1, by etoposide is mediated by p53 and **c-Jun** genes.

AB KAI1 is a metastasis suppressor gene which is capable of inhibiting the processes of tumor metastasis without affecting tumorigenicity per se. We found that etoposide, a **topoisomerase II inhibitor**, is able to activate the expression of the KAI1 gene in a dose-dependent manner in human prostate cancer cell lines, ALVA, DU145, and PC-3 as well as in human lung carcinoma cell A549. The **activation** of the KAI1 gene was mainly mediated by the **c-Jun** gene in the PC-3 and DU145 cell lines, while it was mediated by both p53 and **c-Jun** genes in the A549 cell line. These results suggest that the augmentation of the KAI1 gene expression is independently controlled by p53 and **c-Jun** at the transcriptional level in the human cancer cell lines. Furthermore, treatment of these cell lines with etoposide resulted in significant reduction of cellular invasion measured by the Matrigel invasion chamber. Because etoposide has been shown to be effective on advanced prostate cancer when used in combination with other regimens, our results provide further rationale to use this drug as an antimetastatic agent. (C) 2000 Academic Press.

ACCESSION NUMBER: 2000277910 EMBASE

TITLE: **Activation** of the tumor metastasis suppressor gene, KAI1, by etoposide is mediated by p53 and **c-Jun** genes.

AUTHOR: Mashimo T.; Bandyopadhyay S.; Goodarzi G.; Watabe M.; Pai S.K.; Gross S.C.; Watabe K.

CORPORATE SOURCE: K. Watabe, Dept. Med. Microbiology Immunology, Southern Illinois University, School of Medicine, Springfield, IL 62702, United States. kwatabe@siumed.edu

SOURCE: Biochemical and Biophysical Research Communications, (2 Aug 2000) 274/2 (370-376).
Refs: 25
ISSN: 0006-291X CODEN: BBRCA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

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TI **Activation** of the tumor metastasis suppressor gene, KAI1, by etoposide is mediated by p53 and **c-Jun** genes.

AB KAI1 is a metastasis suppressor gene which is capable of inhibiting the processes of tumor metastasis without affecting tumorigenicity per se. We found that etoposide, a **topoisomerase II inhibitor**, is able to activate the expression of the KAI1 gene in a dose-dependent manner in human prostate cancer cell lines, ALVA, DU145, and PC-3 as well as in human lung carcinoma cell A549. The **activation** of the KAI1 gene was mainly mediated by the **c-Jun** gene in the PC-3 and DU145 cell lines, while it was mediated by both p53 and **c-Jun** genes in the A549 cell line. These results suggest that the augmentation of the KAI1 gene expression is independently controlled by p53 and **c-Jun** at the transcriptional level in the human cancer cell lines. Furthermore, treatment of these cell lines with etoposide resulted in significant reduction of cellular invasion measured by the Matrigel invasion chamber. Because etoposide has been shown to be effective on advanced prostate cancer when used in combination with other regimens, our results provide further rationale to use this drug as an antimetastatic agent.

ACCESSION NUMBER: 2000:416038 BIOSIS

DOCUMENT NUMBER: PREV200000416038

TITLE: **Activation** of the tumor metastasis suppressor

gene, KAI1, by etoposide is mediated by p53 and **c-Jun** genes.

AUTHOR(S): Mashimo, Tomoyuki; Bandyopadhyay, Sucharita; Goodarzi, Goodarz; Watabe, Misako; Pai, Sudha K.; Gross, Steven C.; Watabe, Kounosuke (1)

CORPORATE SOURCE: (1) Department of Medical Microbiology and Immunology, Southern Illinois University School of Medicine, Springfield, IL, 62702 USA

SOURCE: Biochemical and Biophysical Research Communications, (August 2, 2000) Vol. 274, No. 2, pp. 370-376. print. ISSN: 0006-291X.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

L11 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Merbarone, a catalytic inhibitor of DNA topoisomerase II, induces apoptosis in CEM cells through **activation** of ICE/CED-3-like protease.

AB Merbarone (5-(N-phenyl carboxamido)-2-thiobarbituric acid) is an anticancer drug that inhibits the catalytic activity of DNA topoisomerase II (topo II) without damaging DNA or stabilizing DNA-topo II cleavable complexes. Although the cytotoxicity of the complex-stabilizing DNA-topo II inhibitors such as VP-16 (etoposide) has been partially elucidated, the cytotoxicity of merbarone is poorly understood. Here, we report that merbarone induces programmed cell death or apoptosis in human leukemic CEM cells, characterized by internucleosomal DNA cleavage and nuclear condensation. Treatment of CEM cells with apoptosis-inducing concentrations of merbarone caused **activation** of **c-Jun** NH2-terminal kinase/stress-activated protein kinase, **c-jun** gene induction, **activation** of caspase-3/CPP32-like protease but not caspase-1, and the proteolytic cleavage of poly(ADP-ribose) polymerase. Treatment of CEM cells with a potent inhibitor of caspases, Z-Asp-2.6-dichlorobenzoyloxymethyl-ketone, inhibited merbarone-induced caspase-3/CPP32-like activity and apoptosis in a dose-dependent manner. These results indicate that the catalytic inhibition of topo II by merbarone leads to apoptotic cell death through a caspase-3-like protease-dependent mechanism. These results further suggest that **c-Jun** and **c-Jun** NH2-terminal kinase/ stress-activated protein kinase signaling may be involved in the cytotoxicity of merbarone.

ACCESSION NUMBER: 1999:191526 BIOSIS

DOCUMENT NUMBER: PREV199900191526

TITLE: Merbarone, a catalytic inhibitor of DNA topoisomerase II, induces apoptosis in CEM cells through **activation** of ICE/CED-3-like protease.

AUTHOR(S): Khelifa, Tayeb (1); Beck, William T. (1)

CORPORATE SOURCE: (1) Division of Developmental Therapeutics, Cancer Center, College of Medicine, University of Illinois at Chicago, Chicago, IL USA

SOURCE: Molecular Pharmacology, (March, 1999) Vol. 55, No. 3, pp. 548-556. ISSN: 0026-895X.

DOCUMENT TYPE: Article

LANGUAGE: English

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FILE 'MEDLINE, DGENE, EMBASE, WPIDS, BIOSIS, BIOBUSINESS, JICST-EPLUS, FSTA' ENTERED AT 17:49:25 ON 07 MAY 2003

L1 27419 S C-JUN

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L2          4397 S JANUS KINASE
L3           248 S JAK-3
L4         11165 S ARA-C
L5          1457 S TOPOISOMERASE II INHIBITOR
L6         14563 S L1 AND ACTIVATION
L7            91 S L2 AND L3
L8            49 S L7 AND INHIBIT?
L9            40 S L4 AND L6
L10            0 S L9 AND L5
L11            4 S L5 AND L6

=> s l8 and l9
L12            0 L8 AND L9

=> d l8 ti abs ibib 1-12
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L8 ANSWER 1 OF 49 MEDLINE

TI Targeting JAK3 with JANEX-1 for prevention of autoimmune type 1 diabetes in NOD mice.

AB Here we show that **Janus kinase** (**JAK**) **3** is an important molecular target for treatment of autoimmune insulin-dependent (type 1) diabetes mellitus. The rationally designed JAK3 **inhibitor** JANEX-1 exhibited potent immunomodulatory activity and delayed the onset of diabetes in the NOD mouse model of autoimmune type 1 diabetes. Whereas 60% of vehicle-treated control NOD mice became diabetic by 25 weeks, the incidence of diabetes at 25 weeks was only 9% for NOD females treated with daily injections of JANEX-1 (100 mg/kg/day) from Week 10 through Week 25 ($P = 0.007$). Furthermore, JANEX-1 prevented the development of insulitis and diabetes in NOD-scid/scid females after adoptive transfer of splenocytes from diabetic NOD females. Chemical **inhibitors** such as JANEX-1 may provide the basis for effective treatment modalities against human type 1 diabetes. To our knowledge, this is the first report of the immunosuppressive activity of a JAK3 **inhibitor** in the context of an autoimmune disease.

ACCESSION NUMBER: 2003187830 IN-PROCESS
DOCUMENT NUMBER: 22592724 PubMed ID: 12706408
TITLE: Targeting JAK3 with JANEX-1 for prevention of autoimmune type 1 diabetes in NOD mice.
AUTHOR: Cetkovic-Cvrlje Marina; Dragt Angela L; Vassilev Alexei; Liu Xing Ping; Uckun Fatih M
CORPORATE SOURCE: Department of Immunology, Parker Hughes Institute, 2699 Patton Road, St. Paul, 55113, MN, USA.
SOURCE: CLINICAL IMMUNOLOGY, (2003 Mar) 106 (3) 213-25. Journal code: 100883537. ISSN: 1521-6616.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030423
Last Updated on STN: 20030423

L8 ANSWER 2 OF 49 MEDLINE

TI Human immunodeficiency virus-1 envelope glycoproteins and anti-CD4 antibodies **inhibit** interleukin-2-induced Jak/STAT signalling in human CD4 T lymphocytes.

AB Human immunodeficiency virus (HIV) infection leads to a profound T cell dysfunction well before the clinical onset of acquired immunodeficiency syndrome (AIDS). We have been accumulating evidence that one of the mechanisms responsible for this T cell deficiency may be the dysregulation of signal transduction via the interleukin (IL)-2/IL-2 receptor (R) complex. In CD4 T cells, we have observed previously that viral envelope (env) glycoproteins induce IL-2 unresponsiveness and the down-regulation of the three chains making up the IL-2R (alpha, beta, gamma) in vitro. We have now established further that this disruption of the IL-2/IL-2R system

manifests itself in defective signal propagation via the **Janus kinase** (Jak)/signal transducer and activator of transcription (STAT) pathway in response to IL-2. The treatment of CD4 T cells with HIV env or surface ligation of CD4 with anti-CD4 monoclonal antibodies **inhibited** the IL-2-induced activation of Jak-1 and **Jak-3**, as well as their targets, STAT5a and STAT5b. This Jak/STAT deficiency may contribute to the crippling of CD4 T cell responses to a cytokine central to the immune response by HIV.

ACCESSION NUMBER: 2003094601 IN-PROCESS
DOCUMENT NUMBER: 22494436 PubMed ID: 12605694
TITLE: Human immunodeficiency virus-1 envelope glycoproteins and anti-CD4 antibodies **inhibit** interleukin-2-induced Jak/STAT signalling in human CD4 T lymphocytes.
AUTHOR: Kryworuchko M; Pasquier V; Theze J
CORPORATE SOURCE: Unite d'Immunogenetique Cellulaire, Departement de Medecine Moleculaire, Institut Pasteur, Paris, France.
SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (2003 Mar) 131 (3) 422-7.
Journal code: 0057202. ISSN: 0009-9104.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030228
Last Updated on STN: 20030228

L8 ANSWER 3 OF 49 MEDLINE
TI Mechanisms involved in interleukin-15-induced suppression of human neutrophil apoptosis: role of the anti-apoptotic Mcl-1 protein and several kinases including **Janus kinase**-2, p38 mitogen-activated protein kinase and extracellular signal-regulated kinases-1/2.
AB Interleukin-15 (IL-15) is a pro-inflammatory cytokine known as a general **inhibitor** of apoptosis, which possesses potential therapeutic properties. Although IL-15 was previously found to be a human neutrophil agonist, its mode of action remains unknown. Herein, we were interested in elucidating the mechanisms by which it delays neutrophil apoptosis. IL-15 was found to induce tyrosine phosphorylation events and to prevent loss of the anti-apoptotic Mcl-1 protein expression. Using different signal transduction **inhibitors**, we found that **Janus kinase** (Jak)-2, **Jak-3**, p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK), but not G proteins, are involved in IL-15-induced suppression of apoptosis. Furthermore, we found that IL-15 activates Jak-2, p38 MAPK and ERK-1/2, but, unlike granulocyte macrophage-colony-stimulating factor (GM-CSF), it does not activate signal transducer and activator of transcription (STAT)-5a/b. We conclude that IL-15 delays neutrophil apoptosis via several pathways, and that Mcl-1 and several kinases contribute to this. We also conclude that, unlike GM-CSF, IL-15 does not activate the Jak-2/STAT-5 pathway found to be important in neutrophil signaling.

ACCESSION NUMBER: 2002698036 MEDLINE
DOCUMENT NUMBER: 22347259 PubMed ID: 12459483
TITLE: Mechanisms involved in interleukin-15-induced suppression of human neutrophil apoptosis: role of the anti-apoptotic Mcl-1 protein and several kinases including **Janus kinase**-2, p38 mitogen-activated protein kinase and extracellular signal-regulated kinases-1/2.
AUTHOR: Pelletier Martin; Ratthe Claude; Girard Denis
CORPORATE SOURCE: INRS-Institut Armand-Frappier/Sante humaine, Universite du Quebec, 245 boul. Hymus, Pointe-Claire, QC, Canada H9R 1G6.
SOURCE: FEBS LETTERS, (2002 Dec 4) 532 (1-2) 164-70.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030114
Entered Medline: 20030113

L8 ANSWER 4 OF 49 MEDLINE

TI Human lung myofibroblasts as effectors of the inflammatory process: the common receptor gamma chain is induced by Th2 cytokines, and CD40 ligand is induced by lipopolysaccharide, thrombin and TNF-alpha.

AB The common gamma (gamma c) chain, shared by Th1 and Th2 cytokines, is fundamental for the activation of hematopoietic cells, but its role in non-hematopoietic tissues has not been explored. Here we show that in normal lung fibroblasts IL-4 and IL-13 induce the expression of the gamma c chain and its association with **Janus kinase** (**JAK**) **3**, while lung myofibroblasts constitutively express a gamma c chain displaying a limited association with JAK3. In the latter cells, without exogenous cytokines, gamma c/JAK3 controls, through autocrine loops, tyrosine kinase (TYK) 2 phosphorylation and the balance between functional (IL-4Ralpha, IL-13Ralpha 1) and decoy (IL-13Ralpha 2) high-affinity receptors. Moreover, JAK3 is also associated with a pre-phosphorylated IL-4Ralpha and CD40. This novel "heterotrimer" (p-IL-4Ralpha, CD40/JAK3) is functional and controls STAT3 phosphorylation and CD40 expression, as shown by use of the specific JAK3 **inhibitor** WHI-P31. In basal culture conditions, CD40 signaling could be induced by the transient establishment of inter-fibroblastic CD40/CD40 ligand (CD40L) functional bridges. Indeed, powerful pro-inflammatory stimuli such as lipopolysaccharide and thrombin can rapidly mobilize CD40L at the surface of lung myofibroblasts. These interactions are modified by IL-13, which triggers the formation of a new type of functional receptor (p-IL-4Ralpha /IL-13Ralpha 1/gamma c) and also the recruitment and the phosphorylation of JAK3. Treatment with JAK3 **inhibitors** blocks IL-13-induced phosphorylation of JAK2, TYK2 and STAT3, but not of JAK1 and STAT6. These data underline (1) the pivotal role of the gamma c chain, CD40/CD40L, JAK3 and IL-13 in the inflammatory-like activation of lung myofibroblasts, (2) the cell-type restraint effects of IL-13 on these cells, and (3) the potential usefulness of JAK3 **inhibitors** in the treatment of asthma.

ACCESSION NUMBER: 2002448940 MEDLINE
DOCUMENT NUMBER: 22195575 PubMed ID: 12207328
TITLE: Human lung myofibroblasts as effectors of the inflammatory process: the common receptor gamma chain is induced by Th2 cytokines, and CD40 ligand is induced by lipopolysaccharide, thrombin and TNF-alpha.
AUTHOR: Doucet Christelle; Giron-Michel Julien; Canonica Giorgio Walter; Azzarone Bruno
CORPORATE SOURCE: U506 INSERM, Hopital Paul Brousse, Villejuif, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (2002 Sep) 32 (9) 2437-49. Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020904
Last Updated on STN: 20021212
Entered Medline: 20021120

L8 ANSWER 5 OF 49 MEDLINE

TI Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation.

AB Thymic stromal lymphopoietin (TSLP) is a novel cytokine that was found to promote the development of murine B cells in vitro. Here we describe the

cloning and characterization of the human homologue of murine TSLP. This protein, which is expressed in a number of tissues including heart, liver and prostate, prevented apoptosis and stimulated growth of the human acute myeloid leukemia (AML)-derived cell line MUTZ-3. Anti-interleukin (IL)-7 receptor antibodies (Abs) neutralized this effect indicating that TSLP binds to at least part of the IL-7 receptor complex. TSLP induced phosphorylation of signal transducer and activator of transcription (STAT)-5. In contrast to IL-7, TSLP-triggered STAT-5 phosphorylation was not preceded by activation of **janus kinase** ( **JAK**) **3**. These findings would be in accordance with the notion, raised previously for the mouse system, that TSLP leads to STAT-5 phosphorylation by activating other kinases than the JAKs. Some other signaling pathways stimulated by many cytokines are not involved in TSLP activity; thus, TSLP did not stimulate activation of ERK1,2 and p70S6K. Furthermore, neutralizing Abs raised against cytokines known to stimulate the growth of MUTZ-3 cells did not **inhibit** the proliferative effects of TSLP, suggesting that TSLP-induced growth was a direct effect. In summary, we describe the cloning of human TSLP and its proliferative effects on a myeloid cell line. TSLP-induced proliferation is preceded by phosphorylation of STAT-5, but not of **JAK 3**.

ACCESSION NUMBER: 2001433439 MEDLINE
DOCUMENT NUMBER: 21372886 PubMed ID: 11480573
TITLE: Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation.
AUTHOR: Quentmeier H; Drexler H G; Fleckenstein D; Zaborski M; Armstrong A; Sims J E; Lyman S D
CORPORATE SOURCE: DSMZ, German Collection of Microorganisms and Cell Cultures, Department of Human and Animal Cell Cultures, Braunschweig, Germany.
SOURCE: LEUKEMIA, (2001 Aug) 15 (8) 1286-92.
Journal code: 8704895. ISSN: 0887-6924.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816

L8 ANSWER 6 OF 49 MEDLINE
TI Treatment of allergic asthma by targeting **janus kinase** 3-dependent leukotriene synthesis in mast cells with 4-(3', 5'-dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97).
AB 4-(3',5'-Dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97) is a rationally designed potent **inhibitor** of **Janus kinase** (**JAK**)-3. Treatment of mast cells with WHI-P97 **inhibited** the translocation of 5-lipoxygenase (5-LO) from the nucleoplasm to the nuclear membrane and consequently 5-LO-dependent leukotriene (LT) synthesis after IgE receptor/FcepsilonRI crosslinking by >90% at low micromolar concentrations. WHI-P97 did not directly **inhibit** the enzymatic activity of 5-LO, but prevented its translocation to the nuclear membrane without affecting the requisite calcium signal. WHI-P97 was very well tolerated in mice, with no signs of toxicity at dose levels ranging from 5 microg/kg to 50 mg/kg, and LD(10) was not reached at a 50 mg/kg dose level when administered as a single i. p. or i.v. bolus dose. Therapeutic WHI-P97 concentrations, which **inhibit** mast cell leukotriene synthesis in vitro, could easily be achieved in vivo after the i.v. or i.p. administration of a single nontoxic 40 mg/kg bolus dose of WHI-P97. Notably, WHI-P97 showed promising biological activity in a mouse model of allergic asthma at nontoxic dose levels. Treatment of ovalbumin-sensitized mice with WHI-P97 prevented the development of airway hyper-responsiveness to methacholine in a dose-dependent fashion. Furthermore, WHI-P97 **inhibited** the

eosinophil recruitment to the airway lumen after the ovalbumin challenge in a dose-dependent fashion. Further development of WHI-P97 may therefore provide the basis for new and effective treatment as well as prevention programs for allergic asthma in clinical settings.

ACCESSION NUMBER: 2001056701 MEDLINE
DOCUMENT NUMBER: 20536532 PubMed ID: 11082424
TITLE: Treatment of allergic asthma by targeting **janus kinase** 3-dependent leukotriene synthesis in mast cells with 4-(3', 5'-dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97).
AUTHOR: Malaviya R; Chen C L; Navara C; Malaviya R; Liu X P; Keenan M; Waurzyniak B; Uckun F M
CORPORATE SOURCE: Department of Allergy and Inflammatory Diseases, Parker Hughes Institute, St. Paul, Minnesota, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Dec) 295 (3) 912-26.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001220

L8 ANSWER 7 OF 49 MEDLINE
TI Functional uncoupling of the **Janus kinase** 3-Stat5 pathway in malignant growth of human T cell leukemia virus type 1-transformed human T cells.
AB Human T cell leukemia virus type 1 (HTLV-1) transforms cytokine-dependent T lymphocytes and causes adult T cell leukemia. Janus tyrosine kinase ( **Jak**)**3** and transcription factors Stat5a and Stat5b are essential for the proliferation of normal T cells and are constitutively hyperactivated in both HTLV-1-transformed human T cell lines and lymphocytes isolated from HTLV-1-infected patients; therefore, a critical role for the Jak3-Stat5 pathway in the progression of this disease has been postulated. We recently reported that tyrphostin AG-490 selectively blocked IL-2 activation of Jak3/Stat5 and growth of murine T cell lines. Here we demonstrate that disruption of Jak3/Stat5a/b signaling with AG-490 (50 microM) blocked the proliferation of primary human T lymphocytes, but paradoxically failed to **inhibit** the proliferation of HTLV-1-transformed human T cell lines, HuT-102 and MT-2. Structural homologues of AG-490 also **inhibited** the proliferation of primary human T cells, but not HTLV-1-infected cells. Disruption of constitutive Jak3/Stat5 activation by AG-490 was demonstrated by **inhibition** of 1) tyrosine phosphorylation of Jak3, Stat5a (Tyr(694)), and Stat5b (Tyr(699)); 2) serine phosphorylation of Stat5a (Ser(726)) as determined by a novel phosphospecific Ab; and 3) Stat5a/b DNA binding to the Stat5-responsive beta-casein promoter. In contrast, AG-490 had no effect on DNA binding by p50/p65 components of NF-kappaB, a transcription factor activated by the HTLV-1-encoded phosphoprotein, Tax. Collectively, these data suggest that the Jak3-Stat5 pathway in HTLV-1-transformed T cells has become functionally redundant for proliferation. Reversal of this functional uncoupling may be required before Jak3/Stat5 **inhibitors** will be useful in the treatment of this malignancy.

ACCESSION NUMBER: 2001033141 MEDLINE
DOCUMENT NUMBER: 20501115 PubMed ID: 11046040
TITLE: Functional uncoupling of the **Janus kinase** 3-Stat5 pathway in malignant growth of human T cell leukemia virus type 1-transformed human T cells.
AUTHOR: Kirken R A; Erwin R A; Wang L; Wang Y; Rui H; Farrar W L
CORPORATE SOURCE: Department of Integrative Biology and Pharmacology, University of Texas Health Science Center, Houston, TX

77030, USA.. rkirken@farmr1.med.uth.tmc.edu
SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Nov 1) 165 (9) 5097-104.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20021211
Entered Medline: 20001130

L8 ANSWER 8 OF 49 MEDLINE

TI T cell receptor-induced calcineurin activation regulates T helper type 2 cell development by modifying the interleukin 4 receptor signaling complex.

AB The activation of downstream signaling pathways of both T cell receptor (TCR) and interleukin 4 receptor (IL-4R) is essential for T helper type 2 (Th2) cell development, which is central to understanding immune responses against helminthic parasites and in allergic and autoimmune diseases. However, little is known about how these two distinct signaling pathways cooperate with each other to induce Th2 cells. Here, we show that successful Th2 cell development depends on the effectiveness of TCR-induced activation of calcineurin. An **inhibitor** of calcineurin activation, FK506, **inhibited** the in vitro anti-TCR-induced Th2 cell generation in a dose-dependent manner. Furthermore, the development of Th2 cells was significantly impaired in naive T cells from dominant-negative calcineurin Aalpha transgenic mice, whereas that of Th1 cells was less affected. Efficient calcineurin activation in naive T cells upregulated **Janus kinase** ( **Jak**)3 transcription and the amount of protein. The generation of Th2 cells induced in vitro by anti-TCR stimulation was **inhibited** significantly by the presence of Jak3 antisense oligonucleotides, suggesting that the Jak3 upregulation is an important event for the Th2 cell development. Interestingly, signal transducer and activator of transcription (STAT)5 became physically and functionally associated with the IL-4R in the anti-TCR-activated developing Th2 cells that received efficient calcineurin activation, and also in established cloned Th2 cells. In either cell population, the **inhibition** of STAT5 activation resulted in a diminished IL-4-induced proliferation. Moreover, our results suggest that IL-4-induced STAT5 activation is required for the expansion process of developing Th2 cells. Thus, Th2 cell development is controlled by TCR-mediated activation of the Ca(2+)/calcineurin pathway, at least in part, by modifying the functional structure of the IL-4R signaling complex.

ACCESSION NUMBER: 2000298894 MEDLINE
DOCUMENT NUMBER: 20298894 PubMed ID: 10839803
TITLE: T cell receptor-induced calcineurin activation regulates T helper type 2 cell development by modifying the interleukin 4 receptor signaling complex.
AUTHOR: Yamashita M; Katsumata M; Iwashima M; Kimura M; Shimizu C; Kamata T; Shin T; Seki N; Suzuki S; Taniguchi M; Nakayama T
CORPORATE SOURCE: Department of Developmental Immunology, Chiba University School of Medicine, Japan.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2000 Jun 5) 191 (11) 1869-79.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811

Entered Medline: 20000803

L8 ANSWER 9 OF 49 MEDLINE

TI Structure-based design of specific **inhibitors** of **Janus kinase** 3 as apoptosis-inducing antileukemic agents.

AB A novel homology model of the kinase domain of **Janus kinase** (**JAK**) **3** was used for the structure-based design of dimethoxyquinazoline compounds with potent and specific **inhibitory** activity against JAK3. The active site of JAK3 in this homology model measures roughly 8 A x 11 A x 20 A, with a volume of approximately 530 A3 available for **inhibitor** binding. Modeling studies indicated that 4-(phenyl)-amino-6,7-dimethoxyquinazoline (parent compound WHI-258) would likely fit into the catalytic site of JAK3 and that derivatives of this compound that contain an OH group at the 4' position of the phenyl ring would more strongly bind to JAK3 because of added interactions with Asp-967, a key residue in the catalytic site of JAK3. These predictions were consistent with docking studies indicating that compounds containing a 4'-OH group, WHI-P131 [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline], WHI-P154 [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], and WHI-P97 [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazolin e], were likely to bind favorably to JAK3, with estimated K(i)s ranging from 0.6 to 2.3 microM. These compounds **inhibited** JAK3 in immune complex kinase assays in a dose-dependent fashion. In contrast, compounds lacking the 4'-OH group, WHI-P79 [4-(3'-bromophenyl)-amino-6,7-dimethoxyquinazoline], WHI-P111 [4-(3'-bromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline], WHI-P112 [4-(2',5'-dibromophenyl)-amino-6,7-dimethoxyquinazoline], WHI-P132 [4-(2'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], and WHI-P258 [4-(phenyl)-amino-6,7-dimethoxyquinazoline], were predicted to bind less strongly, with estimated K(i)s ranging from 28 to 72 microM. These compounds did not show any significant JAK3 **inhibition** in kinase assays. Furthermore, the lead dimethoxyquinazoline compound, WHI-P131, which showed potent JAK3-**inhibitory** activity (IC50 of 78 microM), did not **inhibit** JAK1 and JAK2, the ZAP/SYK family tyrosine kinase SYK, the TEC family tyrosine kinase BTK, the SRC family tyrosine kinase LYN, or the receptor family tyrosine kinase insulin receptor kinase, even at concentrations as high as 350 microM. WHI-P131 induced apoptosis in JAK3-expressing human leukemia cell lines NALM-6 and LC1;19 but not in melanoma (M24-MET) or squamous carcinoma (SQ20B) cells. Leukemia cells were not killed by dimethoxyquinazoline compounds that were inactive against JAK3. WHI-P131 **inhibited** the clonogenic growth of JAK3-positive leukemia cell lines DAUDI, RAMOS, LC1;19, NALM-6, MOLT-3, and HL-60 (but not JAK3-negative BT-20 breast cancer, M24-MET melanoma, or SQ20B squamous carcinoma cell lines) in a concentration-dependent fashion. Potent and specific **inhibitors** of JAK3 such as WHI-P131 may provide the basis for the design of new treatment strategies against acute lymphoblastic leukemia, the most common form of childhood cancer.

ACCESSION NUMBER: 1999316808 MEDLINE
DOCUMENT NUMBER: 99316808 PubMed ID: 10389946
TITLE: Structure-based design of specific **inhibitors** of **Janus kinase** 3 as apoptosis-inducing antileukemic agents.
AUTHOR: Sudbeck E A; Liu X P; Narla R K; Mahajan S; Ghosh S; Mao C; Uckun F M
CORPORATE SOURCE: Department of Structural Biology, Hughes Institute, St. Paul, Minnesota 55113, USA.
SOURCE: CLINICAL CANCER RESEARCH, (1999 Jun) 5 (6) 1569-82. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991012

Last Updated on STN: 19991012
Entered Medline: 19990930

L8 ANSWER 10 OF 49 MEDLINE
TI Genetic and biochemical evidence for a critical role of **Janus kinase (JAK)-3** in mast cell-mediated type I hypersensitivity reactions.
AB We investigated the role of JAK3 in IgE receptor/FcepsilonRI-mediated mast cell responses. IgE/antigen induced degranulation and mediator release were substantially reduced with Jak3-/- mast cells from JAK3-null mice that were generated by targeted disruption of Jak3 gene in embryonic stem cells. Further, treatment of mast cells with 3'bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154), a potent **inhibitor** of JAK3, **inhibited** degranulation and proinflammatory mediator release after IgE receptor/ FcepsilonRI crosslinking. Thus, JAK3 plays a pivotal role in IgE receptor/ FcepsilonRI-mediated mast cell responses and targeting JAK3 may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions.

ACCESSION NUMBER: 1999225310 MEDLINE
DOCUMENT NUMBER: 99225310 PubMed ID: 10208864
TITLE: Genetic and biochemical evidence for a critical role of **Janus kinase (JAK)-3** in mast cell-mediated type I hypersensitivity reactions.
AUTHOR: Malaviya R; Uckun F M
CORPORATE SOURCE: Department of Allergy, Hughes Institute, St. Paul, Minnesota, USA.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Apr 21) 257 (3) 807-13.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990601

L8 ANSWER 11 OF 49 MEDLINE
TI Interleukin (IL)-15 induces survival and proliferation of the growth factor-dependent acute myeloid leukemia M-07e through the IL-2 receptor beta/gamma.
AB We have analyzed the effects of IL-15, a growth factor with IL-2-like properties produced by dendritic and stromal cells, on 3 GM-CSF/IL-3-dependent AML cell lines: M-07e, UT-7 and TF-1. M-07e cells proliferated in response to IL-15, while UT-7 and TF-1 cells failed to respond. In addition, IL-15 supported long-term proliferation of M-07e cells, thus allowing selection of a subline (M-07SB), which displayed an enhanced sensitivity to IL-15. M-07e and M-07SB cells undergo apoptosis following 48-hr growth factor (GM-CSF or IL-15) starvation, as detected by cytofluorimetric analysis and DNA laddering. IL-15 (20 ng/ml) prevented apoptosis in both cell lines. M-07e and M-07SB expressed IL-2R beta, IL-2R gamma, Jak-1 and **Jak-3** mRNA, while IL-15R alpha mRNA was undetectable. In contrast, IL-15R alpha was expressed in UT-7 and TF-1 cells, which lacked expression of IL-2R beta mRNA and, in the case of UT-7, also of **Jak-3** mRNA. Accordingly, surface IL-2R beta protein was identified only in M-07e and M-07SB cells, by indirect immunofluorescence, while no expression of IL-2R alpha and IL-15R alpha was detected. Anti-IL-2R beta antibodies (10 microg/ml) efficiently blocked (90% **inhibition**) the proliferation and the anti-apoptotic effect induced by IL-15, while anti-GM-CSFR alpha antibodies had no effect. Anti-IL-2R gamma antibodies were less efficient at proliferation **inhibition** but synergized with suboptimal

concentrations of anti-IL-2R beta antibodies. Our data suggest a role of IL-15 as an anti-apoptotic and mitogenic growth factor for a subset of myeloid leukemias expressing a functional IL-2R beta/gamma complex.

ACCESSION NUMBER: 1998425622 MEDLINE
DOCUMENT NUMBER: 98425622 PubMed ID: 9754651
TITLE: Interleukin (IL)-15 induces survival and proliferation of the growth factor-dependent acute myeloid leukemia M-07e through the IL-2 receptor beta/gamma.
AUTHOR: Meazza R; Basso S; Gaggero A; Detotero D; Trentin L; Pereno R; Azzarone B; Ferrini S
CORPORATE SOURCE: Istituto Nazionale per la Ricerca sul Cancro, Centro di Biotecnologie Avanzate, Genoa, Italy.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1998 Oct 5) 78 (2) 189-95.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981009

L8 ANSWER 12 OF 49 MEDLINE
TI Role of tyrosine kinases in induction of the c-jun proto-oncogene in irradiated B-lineage lymphoid cells.
AB Exposure of B-lineage lymphoid cells to ionizing radiation induces an elevation of c-jun proto-oncogene mRNA levels. This signal is abrogated by protein-tyrosine kinase (PTK) **inhibitors**, indicating that activation of an as yet unidentified PTK is mandatory for radiation-induced c-jun expression. Here, we provide experimental evidence that the cytoplasmic tyrosine kinases BTK, SYK, and LYN are not required for this signal. Lymphoma B-cells rendered deficient for LYN, SYK, or both by targeted gene disruption showed increased c-jun expression levels after radiation exposure, but the magnitude of the stimulation was lower than in wild-type cells. Thus, these PTKs may participate in the generation of an optimal signal. Notably, an **inhibitor** of **JAK-3** (Janus family kinase-3) abrogated radiation-induced c-jun activation, prompting the hypothesis that a chicken homologue of **JAK-3** may play a key role in initiation of the radiation-induced c-jun signal in B-lineage lymphoid cells.

ACCESSION NUMBER: 1998316346 MEDLINE
DOCUMENT NUMBER: 98316346 PubMed ID: 9651374
TITLE: Role of tyrosine kinases in induction of the c-jun proto-oncogene in irradiated B-lineage lymphoid cells.
AUTHOR: Goodman P A; Niehoff L B; Uckun F M
CORPORATE SOURCE: Department of Molecular Genetics, Wayne Hughes Institute, St. Paul, Minnesota 55113, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jul 10) 273 (28) 17742-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980806

=> d his

(FILE 'HOME' ENTERED AT 17:48:32 ON 07 MAY 2003)

FILE 'MEDLINE, DGENE, EMBASE, WPIDS, BIOSIS, BIOBUSINESS, JICST-EPLUS, FSTA' ENTERED AT 17:49:25 ON 07 MAY 2003

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L1         27419 S C-JUN
L2          4397 S JANUS KINASE
L3           248 S JAK-3
L4         11165 S ARA-C
L5          1457 S TOPOISOMERASE II INHIBITOR
L6         14563 S L1 AND ACTIVATION
L7            91 S L2 AND L3
L8            49 S L7 AND INHIBIT?
L9            40 S L4 AND L6
L10            0 S L9 AND L5
L11            4 S L5 AND L6
L12            0 S L8 AND L9
```

=> d l9 ti abs ibib 1-15

L9 ANSWER 1 OF 40 MEDLINE

TI Role of **c-Jun** N-terminal kinase/p38 stress signaling in 1-beta-D-arabinofuranosylcytosine-induced apoptosis.

AB 1-beta-D-Arabinofuranosylcytosine (**ara-C**) induced apoptosis in HL-60 cells, which was preceded by the **activation** of extracellular signal-regulated kinase (ERK), **c-Jun** N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 mitogen-activated protein kinase (MAPK). 2'-Amino-3'-methoxyflavone (PD098059) and 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole (SB203580) were used to inhibit the activity of ERK and p38, respectively. SEK-AL, a dominant-negative mutant of SEK1, was transfected into HL-60 cells (HL-60/SEK-AL) to assess the role of JNK/SAPK activity in apoptosis. PD098059 (25 microM) inhibited **ara-C**-induced caspase-3-like activity but was ineffective in altering **ara-C**-mediated apoptotic DNA fragmentation and clonogenicity. On the other hand, SB203580 (20 microM) inhibited **ara-C**-induced caspase-3-like activity, apoptotic DNA fragmentation, and clonogenicity. The inhibition of JNK1 **activation** in HL-60/SEK-AL cells did not block **ara-C**-induced apoptotic DNA fragmentation. These results suggest that **ara-C**-induced apoptotic DNA fragmentation and loss of clonogenicity occur through a p38-dependent pathway.


ACCESSION NUMBER: 2000106865 MEDLINE
DOCUMENT NUMBER: 20106865 PubMed ID: 10644049


TITLE: Role of **c-Jun** N-terminal kinase/p38 stress signaling in 1-beta-D-arabinofuranosylcytosine-induced apoptosis.


AUTHOR: Stadheim T A; Saluta G R; Kucera G L

CORPORATE SOURCE: Comprehensive Cancer Center of Wake Forest University School of Medicine, Department of Physiology and Pharmacology, Winston-Salem, NC 27157, USA.



CONTRACT NUMBER: R29 CA58944 (NCI)
T32 CA09433 (NCI)

SOURCE: BIOCHEMICAL PHARMACOLOGY, (2000 Feb 15) 59 (4) 407-18. Journal code: 0101032. ISSN: 0006-2952.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200002

ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000203

L9 ANSWER 2 OF 40 MEDLINE

TI The mechanism of **Ara-C**-induced apoptosis of differentiating cerebellar granule neurons.

AB Neurotoxicity is one of the side-effects of the therapeutically useful antitumour agent, **Ara-C** (or 1-beta-d-arabinofuranosyl-cytosine, cytarabine). This agent is also reported to induce cell death of cultured neurons. In this study, we show that **Ara-C** -induced death of differentiating rat cerebellar granule neurons is prevented by cycloheximide at concentrations corresponding to its action in preventing protein synthesis. The death is accompanied by cleavage of the caspase substrate poly ADP ribose polymerase (PARP) and c-Abl-dependent **activation** of the stress-activated protein kinases **c-Jun** N-terminal kinase and p38. However, **c-Jun** levels do not rise and the **activation** of the stress-activated protein kinases is not required for this form of neuronal death. Cyclin-dependent kinase (cdk) activity and inappropriate cell-cycle re-entry have been implicated in some forms of death in differentiated neurons. Here we show that **Ara-C** -induced death of cerebellar granule neurons is prevented by an inhibitor of cdk4, whereas inhibition of cdk1, -2 and -5 mimics the death, and non-cdk4/6 cdks are inhibited by **Ara-C** treatment. Cdk1 and -2 are dramatically down-regulated during neuronal differentiation, and neither **Ara-C** nor inhibition of these cdks induces death in mature neurons. This mechanism could also play a significant role in the neurotoxicity associated with the therapeutic use of **Ara-C**, as cdk levels can be upregulated in stressed neurons of adult brain. We propose that the balance between cdk4/6 and cdk1/2/5 activity may determine the survival of early differentiating neurons, and that DNA-damaging agents may induce neuronal death by inhibiting cdk1/2/5 under conditions which require these activities for survival.

ACCESSION NUMBER: 1999203333 MEDLINE
DOCUMENT NUMBER: 99203333 PubMed ID: 10103100
TITLE: The mechanism of **Ara-C**-induced apoptosis of differentiating cerebellar granule neurons.
AUTHOR: Courtney M J; Coffey E T
CORPORATE SOURCE: Department of Biochemistry, Abo Akademi University, BioCity, Turku, Finland.. mcourtne@aton.abo.fi
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (1999 Mar) 11 (3) 1073-84.
Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 20030118
Entered Medline: 19990426

L9 ANSWER 3 OF 40 MEDLINE

TI Effects of **Ara-C** on neutral sphingomyelinase and mitogen- and stress-activated protein kinases in T-lymphocyte cell lines.

AB Neutral sphingomyelinase (SMase) can be activated by extracellular signals to produce ceramide, which may affect mitogen-activated protein kinase (MAPK) activities. Neutral SMase activity was assessed in membranes from Jurkat, a human T-cell line, and EL4, a murine T-cell line. **Ara -C** activated SMase with 10 minutes in both Jurkat and EL4 cells, while phorbol ester (PMA) had no effect. PMA, but not **Ara-C** or ceramides, activated ERK MAPKS, in Jurkat and EL4. PMA acted synergistically with ionomycin to activate JNK MAPKs in Jurkat and EL4 within 10 minutes. **Ara-C** activated JNKs only after prolonged incubation (90-120 minutes). Thus, ceramide is not a positive signal for ERK **activation** in T-cell lines. The effects of

**Ara-C** on JNK activity may be mediated through secondary response pathways.

ACCESSION NUMBER: 97107281 MEDLINE
DOCUMENT NUMBER: 97107281 PubMed ID: 8950029
TITLE: Effects of **Ara-C** on neutral sphingomyelinase and mitogen- and stress-activated protein kinases in T-lymphocyte cell lines.
AUTHOR: Bradshaw C D; Ella K M; Thomas A L; Qi C; Meier K E
CORPORATE SOURCE: Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston 29425, USA.
CONTRACT NUMBER: CA58640-04 (NCI)
HL 07260 (NHLBI)
SOURCE: BIOCHEMISTRY AND MOLECULAR BIOLOGY INTERNATIONAL, (1996 Nov) 40 (4) 709-19.
Journal code: 9306673. ISSN: 1039-9712.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970422
Last Updated on STN: 19980206
Entered Medline: 19970408

L9 ANSWER 4 OF 40 MEDLINE
TI Involvement of stress-activated protein kinase in the cellular response to 1-beta-D-arabinofuranosylcytosine and other DNA-damaging agents.
AB The cellular response to 1-beta-D-arabinofuranosylcytosine (**ara-C**) includes **activation** of Jun/AP-1, induction of **c-jun** transcription, and programmed cell death. The stress-activated protein (SAP) kinases stimulate the transactivation function of **c-jun** by amino terminal phosphorylation. The present work demonstrates that **ara-C** activates p54 SAP kinase. The finding that SAP kinase is also activated by alkylating agents (mitomycin C and cisplatinum) and the topoisomerase I inhibitor 9-amino-camptothecin supports DNA damage as an initial signal in this cascade. The results demonstrate that **ara-C** also induces binding of SAP kinase to the SH2/SH3-containing adapter protein Grb2. SAP kinase binds to the SH3 domains of Grb2, while interaction of the p85 alpha-subunit of phosphatidylinositol 3-kinase complex. The results also demonstrate that **ara-C** treatment is associated with inhibition of lipid and serine kinase activities of PI 3-kinase. The potential significance of the **ara-C** -induced interaction between SAP kinase and PI 3-kinase is further supported by the demonstration that Wortmannin, an inhibitor of PI 3-kinase, stimulates SAP kinase activity. The finding that Wortmannin treatment is also associated with internucleosomal DNA fragmentation may support a potential link between PI 3-kinase and regulation of both SAP kinase and programmed cell death.

ACCESSION NUMBER: 96192344 MEDLINE
DOCUMENT NUMBER: 96192344 PubMed ID: 9019171
TITLE: Involvement of stress-activated protein kinase in the cellular response to 1-beta-D-arabinofuranosylcytosine and other DNA-damaging agents.
AUTHOR: Saleem A; Datta R; Yuan Z M; Kharbanda S; Kufe D
CORPORATE SOURCE: Division of Cancer Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: CA29431 (NCI)
SOURCE: CELL GROWTH AND DIFFERENTIATION, (1995 Dec) 6 (12) 1651-8.
Journal code: 9100024. ISSN: 1044-9523.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19980206
Entered Medline: 19970211

L9 ANSWER 5 OF 40 MEDLINE
TI c-Abl **activation** regulates induction of the SEK1/stress-activated protein kinase pathway in the cellular response to 1-beta-D-arabinofuranosylcytosine.
AB Previous work has shown that treatment of cells with the antimetabolite 1-beta-D-arabinofuranosylcytosine (**ara-C**) is associated with induction of the **c-jun** gene. The present studies demonstrate that **ara-C** activates the c-Abl non-receptor tyrosine kinase. We also demonstrate that activity of the stress-activated protein kinase (SAP kinase/JNK) is increased in **ara-C**-treated cells. Using cells deficient in c-Abl (Abl-/-) and after introduction of the c-abl gene, we show that **ara-C**-induced c-Abl activity is necessary for the stimulation of SAP kinase. Other studies using cells transfected with a SEK1 dominant negative demonstrate that **ara-C**-induced SAP kinase activity is SEK1-dependent. Furthermore, we show that overexpression of truncated c-Abl results in **activation** of the SEK1/SAP kinase cascade.
ACCESSION NUMBER: 96107171 MEDLINE
DOCUMENT NUMBER: 96107171 PubMed ID: 8530447
TITLE: c-Abl **activation** regulates induction of the SEK1/stress-activated protein kinase pathway in the cellular response to 1-beta-D-arabinofuranosylcytosine.
AUTHOR: Kharbanda S; Pandey P; Ren R; Mayer B; Zon L; Kufe D
CORPORATE SOURCE: Division of Cancer Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: CA29431 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Dec 22) 270 (51) 30278-81.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960220
Last Updated on STN: 19970203
Entered Medline: 19960130

L9 ANSWER 6 OF 40 MEDLINE
TI Augmentation by aphidicolin of 1-beta-D-arabinofuranosylcytosine-induced **c-jun** and NF-kappa B **activation** in a human myeloid leukemia cell line: correlation with apoptosis.
AB 1-beta-D-arabinofuranosylcytosine (**ara-C**) (2 microM) can induce apoptosis in a human myeloid leukemia cell line, U937, after 4 h of incubation. Pretreatment of cells with aphidicolin (2 microM) augments **ara-C**-induced apoptosis, since it was first observed at 0.4 microM **ara-C** and became more intense at 2 and 10 microM. Although aphidicolin itself had a marginal effect on **c-jun** expression, it significantly augmented **ara -C** induced **c-jun** upregulation by shortening the lag time and lowering **ara-C** concentrations necessary for the induction of detectable **c-jun** transcripts. Aphidicolin and **ara-C** acted synergistically to increase NF-kappa B DNA binding activity as determined by an electrophoretic mobility shift assay. Expression of c-myc was

slightly increased through the DNA degradative phase, and was then downregulated. Thus, the **activation** of NF-kappa B and **c-jun** expression seems to be well correlated with the potentiation by aphidicolin of **ara-C**-induced apoptosis.

ACCESSION NUMBER: 96033081 MEDLINE
DOCUMENT NUMBER: 96033081 PubMed ID: 7564475
TITLE: Augmentation by aphidicolin of 1-beta-D-arabinofuranosylcytosine-induced **c-jun** and NF-kappa B **activation** in a human myeloid leukemia cell line: correlation with apoptosis.
AUTHOR: Kuwakado K; Kubota M; Bessho R; Kataoka A; Usami I; Lin Y W; Okuda A; Wakazono Y
CORPORATE SOURCE: Department of Pediatrics, Faculty of Medicine, Kyoto University, Japan.
SOURCE: LEUKEMIA RESEARCH, (1995 Sep) 19 (9) 645-50. Journal code: 7706787. ISSN: 0145-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19970203
Entered Medline: 19951122

L9 ANSWER 7 OF 40 MEDLINE
TI 1-beta-D-arabinofuranosylcytosine activates serine/threonine protein kinases and **c-jun** gene expression in phorbol ester-resistant myeloid leukemia cells.
AB 1-beta-D-Arabinofuranosylcytosine (**ara-C**) is an effective antileukemic agent that misincorporates into DNA. Recent studies have demonstrated that **ara-C** treatment is associated with transient induction of the **c-jun** early response gene. The present studies have examined the effects of **ara-C** on **c-jun** expression in a phorbol ester-resistant variant of the HL-60 myeloid leukemia cell line, designated HL-525, that is deficient in protein kinase C (PKC)-mediated signal transduction and fails to respond to 12-O-tetradecanoylphorbol-13-acetate with induction of **c-jun** transcripts. The results demonstrate that treatment of HL-525 cells with **ara-C** is associated with transcriptional **activation** of the **c-jun** gene. We also demonstrate that **ara-C** treatment is associated with **activation** of a PKC-like activity. Partial purification of this Ca(2+)-independent activity has demonstrated phosphorylation of synthetic peptides derived from (a) amino acids 4-14 of myelin basic protein and (b) the pseudosubstrate region of PKC (amino acids 19-31), with substitution of Ala25 with serine. The finding that the **ara-C**-induced activity is inhibited by the pseudosubstrate PKC(19-36) supports the **activation** of a PKC-like enzyme. Because PKC can act upstream of the mitogen-activated protein (MAP) kinases, we studied the effects of **ara-C** treatment on MAP kinase activity. The results demonstrate that MAP kinase is activated in **ara-C**-treated cells and that the kinetics of this **activation** are similar to those of the PKC-like activity. Because 12-O-tetradecanoylphorbol-13-acetate has little, if any, effect on the PKC-like and MAP kinase activities in HL-525 cells, these findings suggest that **ara-C** activates a distinct signaling cascade that may contribute to induction of the **c-jun** gene.

ACCESSION NUMBER: 94335904 MEDLINE
DOCUMENT NUMBER: 94335904 PubMed ID: 8058058
TITLE: 1-beta-D-arabinofuranosylcytosine activates serine/threonine protein kinases and **c-**

jun gene expression in phorbol ester-resistant myeloid leukemia cells.
AUTHOR: Kharbanda S; Emoto Y; Kisaki H; Saleem A; Kufe D
CORPORATE SOURCE: Division of Cancer Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115.
CONTRACT NUMBER: CA29431 (NCI)
CA42802 (NCI)
SOURCE: MOLECULAR PHARMACOLOGY, (1994 Jul) 46 (1) 67-72.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940920
Last Updated on STN: 19970203
Entered Medline: 19940909

L9 ANSWER 8 OF 40 MEDLINE
TI **Activation** of the jun-D gene during treatment of human myeloid leukemia cells with 1-beta-D-arabinofuranosylcytosine.
AB The jun-D gene is a member of the **c-jun** family of early response genes that code for DNA binding proteins. The present studies demonstrate that 1-beta-D-arabinofuranosylcytosine (**ara-C**) increases jun-D expression in HL-525 myeloid leukemia cells. This induction by **ara-C** was maximal at 6 hr and transient. In contrast, **ara-C** had no detectable effect on the gene coding for the cAMP-responsive element binding protein 1. Nuclear run-on assays demonstrated that **ara-C** treatment is associated with an increased rate of jun-D transcription. The results also show that jun-D transcripts are stabilized at a posttranscriptional level in **ara-C**-treated cells. Taken together, these results demonstrate that **ara-C** induces expression of the jun-D gene and that this effect is regulated by transcriptional and posttranscriptional mechanisms.
ACCESSION NUMBER: 93290695 MEDLINE
DOCUMENT NUMBER: 93290695 PubMed ID: 8512587
TITLE: **Activation** of the jun-D gene during treatment of human myeloid leukemia cells with 1-beta-D-arabinofuranosylcytosine.
AUTHOR: Kharbanda S; Huberman E; Kufe D
CORPORATE SOURCE: Laboratory of Clinical Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115.
CONTRACT NUMBER: CA29431 (NCI)
CA42802 (NCI)
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1993 May 25) 45 (10) 2055-61.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930723
Last Updated on STN: 20021015
Entered Medline: 19930709

L9 ANSWER 9 OF 40 MEDLINE
TI **Activation** of the AP-1 transcription factor by arabinofuranosylcytosine in myeloid leukemia cells.
AB Previous studies have shown that 1-beta-D-arabinofuranosylcytosine ( **ara-C**) induces transcription of the **c-jun** immediate early response gene in human myeloid leukemia cells. The present work has examined the mechanisms responsible for this effect.

Deleted forms of the **c-jun** promoter were linked to the chloramphenicol acetyltransferase (CAT) gene and transfected into KG-1 cells. The results demonstrate that **ara-C**-induced **c-jun** transcription is mediated by an element between positions -74 and -20 upstream to the start site. Electrophoretic mobility shift assays with the fragment f(-74/-20) showed an increase in binding with nuclear proteins from **ara-C**-treated cells as compared with untreated cells. Competition with an oligonucleotide containing the AP-1 consensus sequence indicated that **ara-C** stimulates binding of nuclear proteins at the AP-1 site in the **c-jun** promoter. These findings were confirmed in other gel shift studies with the collagenase enhancer AP-1 consensus sequence and with a DNA fragment containing an altered AP-1 site. The binding of JUN/AP-1 was maximal at 1 hour of **ara-C** treatment and decreased to baseline levels at 12 hours. The finding that **ara-C** induces AP-1 binding in the absence of protein synthesis indicated that this agent activates already synthesized JUN/AP-1. To confirm these findings, the AP-1 consensus sequence was introduced 5' to the heterologous SV40 promoter. The results show that AP-1 enhances SV40 promoter activity in **ara-C**-treated cells. Taken together, these findings indicate that: (1) enhancement of JUN/AP-1 activity in **ara-C**-treated cells involves a posttranslational modification of JUN/AP-1; and (2) binding of activated JUN/AP-1 to the AP-1 site in the **c-jun** promoter confers **ara-C** inducibility of this gene.


ACCESSION NUMBER: 92119295 MEDLINE
DOCUMENT NUMBER: 92119295 PubMed ID: 1310062

TITLE: **Activation** of the AP-1 transcription factor by arabinofuranosylcytosine in myeloid leukemia cells.

COMMENT: Retraction in: Blood 1999 May 15;93(10):3573


AUTHOR: Brach M A; Herrmann F; Kufe D W
CORPORATE SOURCE: Laboratory of Clinical Pharmacology, Dana-Farber Cancer Institute, Boston, MA 02115.


CONTRACT NUMBER: CA29431 (NCI)
SOURCE: BLOOD, (1992 Feb 1) 79 (3) 728-34.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RETRACTED PUBLICATION)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920315
Last Updated on STN: 20001012
Entered Medline: 19920227


L9 ANSWER 10 OF 40 MEDLINE

TI Regulation of **c-jun** gene expression in HL-60 leukemia cells by 1-beta-D-arabinofuranosylcytosine. Potential involvement of a protein kinase C dependent mechanism.


AB 1-beta-D-Arabinofuranosylcytosine (**ara-C**) is an effective chemotherapeutic agent that incorporates into DNA and results in DNA fragmentation. Recent work has demonstrated that **ara-C** transiently induces expression of the **c-jun** immediate early response gene. The present studies in HL-60 myeloid leukemia cells extend these findings by demonstrating that the increase in **c-jun** mRNA levels at 6 h of **ara-C** treatment is regulated by a transcriptional mechanism. In contrast, the subsequent down-regulation of **c-jun** expression is controlled by a posttranscriptional decrease in the stability of the **c-jun** transcripts. Previous work in phorbol ester treated cells has indicated that **c-jun** expression is regulated by the **activation** of protein kinase C. The present results demonstrate that protein kinase C activity is increased in

**ara-C**-treated cells. This increase was maximal at 60 min and remained detectable through 6 h of **ara-C** exposure. Moreover, the induction of **c-jun** transcripts by **ara-C** was inhibited by the isoquinolinesulfonamide derivative H7, but not by HA1004, suggesting that this effect is mediated by protein kinase C. **Ara-C** -induced **c-jun** expression was also inhibited by staurosporine, another inhibitor of protein kinase C. Taken together, these results indicate that the cellular response to **ara-C** includes the **activation** of protein kinase C and that **ara-C** potentially induces **c-jun** transcription by a protein kinase C dependent signaling mechanism.

ACCESSION NUMBER: 91329367 MEDLINE
DOCUMENT NUMBER: 91329367 PubMed ID: 1907849
TITLE: Regulation of **c-jun** gene expression in HL-60 leukemia cells by 1-beta-D-arabinofuranosylcytosine. Potential involvement of a protein kinase C dependent mechanism.
AUTHOR: Kharbanda S; Datta R; Kufe D
CORPORATE SOURCE: Laboratory of Clinical Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115.
CONTRACT NUMBER: CA29431 (NCI)
SOURCE: BIOCHEMISTRY, (1991 Aug 13) 30 (32) 7947-52. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911006
Last Updated on STN: 19970203
Entered Medline: 19910913

L9 ANSWER 11 OF 40 DGENE (C) 2003 THOMSON DERWENT
TI New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
AN AAZ87412 DNA DGENE
AB The invention relates to a method of inhibiting **c-jun** proto-oncogene expression in mammalian or avian cells by contacting the cells with a compound that inhibits the activity of Janus family kinase 3 (JAK-3). It also encompasses quinazoline compounds and pharmaceutically acceptable salts thereof, which are capable of selectively inhibiting the activity of JAK-3, but not JAK-1 or JAK-2. JAK kinases play a key role in the JAK/STAT (signal transducers and activators of transcription) signalling pathway. JAK kinases phosphorylate STAT proteins, which in turn causes dimerisation of the STAT proteins. The STAT complexes then translocate to the nucleus where they enhance the transcription of target genes (e.g., **c-jun**). The methods and compounds of the invention may be used to prevent or treat pathological conditions in mammalian or avian cells where **c-jun** **activation** is implicated. Factors which activate **c-jun** include exposure to radiation or to chemical agents that cause DNA damage (e.g., **ara-C**, topoisomerase II inhibitors or alkylating agents). Conditions that may be treated include tissue or organ damage, inflammation, hair loss or the negative effects produced by oxygen free radicals during chemotherapy. The methods and compounds may also be used to treat conditions resulting from the action of internally generated oxygen free radicals, such conditions including ageing and amyelotrophic lateral sclerosis (ALS). Sequences AAZ87407-Z87412 represent PCR primers used in an exemplification of the invention to generate hybridisation probes for use in Northern blot analysis of RNA extracted from irradiated DT-40 chicken lymphoma B-cells. The cells had previously been treated with a JAK-3-specific inhibitor or

a general protein tyrosine kinase inhibitor (genistein). Primers AAZ87407-Z87408 were used to amplify a 506 bp JAK-3 probe from chicken genomic DNA. Reverse transcriptase-PCR primer pairs AAZ87409-Z87410 and AAZ87411-Z87412 were used to amplify a 538 bp GAPDH (glyceraldehyde-3-phosphate dehydrogenase) control probe and a 413 bp beta-actin control probe respectively from chicken RNA.

ACCESSION NUMBER: AAZ87412 DNA DGENE
TITLE: New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
INVENTOR: Uckun F M
PATENT ASSIGNEE: (HUGH-N) HUGHES INST.
(UCKU-I) UCKUN F M.
PATENT INFO: WO 2000000202 A1 20000106 49p
APPLICATION INFO: WO 1999-US14923 19990630
PRIORITY INFO: US 1998-91150 19980630
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-170884 [15]
DESCRIPTION: Chicken beta-actin RT-PCR primer, SEQ ID NO:6.

L9 ANSWER 12 OF 40 DGENE (C) 2003 THOMSON DERWENT
TI New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
AN AAZ87411 DNA DGENE
AB The invention relates to a method of inhibiting **c-jun** proto-oncogene expression in mammalian or avian cells by contacting the cells with a compound that inhibits the activity of Janus family kinase 3 (JAK-3). It also encompasses quinazoline compounds and pharmaceutically acceptable salts thereof, which are capable of selectively inhibiting the activity of JAK-3, but not JAK-1 or JAK-2. JAK kinases play a key role in the JAK/STAT (signal transducers and activators of transcription) signalling pathway. JAK kinases phosphorylate STAT proteins, which in turn causes dimerisation of the STAT proteins. The STAT complexes then translocate to the nucleus where they enhance the transcription of target genes (e.g., **c-jun**). The methods and compounds of the invention may be used to prevent or treat pathological conditions in mammalian or avian cells where **c-jun** **activation** is implicated. Factors which activate **c-jun** include exposure to radiation or to chemical agents that cause DNA damage (e.g., **ara-C**, topoisomerase II inhibitors or alkylating agents). Conditions that may be treated include tissue or organ damage, inflammation, hair loss or the negative effects produced by oxygen free radicals during chemotherapy. The methods and compounds may also be used to treat conditions resulting from the action of internally generated oxygen free radicals, such conditions including ageing and amyelotrophic lateral sclerosis (ALS). Sequences AAZ87407-Z87412 represent PCR primers used in an exemplification of the invention to generate hybridisation probes for use in Northern blot analysis of RNA extracted from irradiated DT-40 chicken lymphoma B-cells. The cells had previously been treated with a JAK-3-specific inhibitor or a general protein tyrosine kinase inhibitor (genistein). Primers AAZ87407-Z87408 were used to amplify a 506 bp JAK-3 probe from chicken genomic DNA. Reverse transcriptase-PCR primer pairs AAZ87409-Z87410 and AAZ87411-Z87412 were used to amplify a 538 bp GAPDH (glyceraldehyde-3-phosphate dehydrogenase) control probe and a 413 bp beta-actin control probe respectively from chicken RNA.

ACCESSION NUMBER: AAZ87411 DNA DGENE
TITLE: New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
INVENTOR: Uckun F M
PATENT ASSIGNEE: (HUGH-N) HUGHES INST.
(UCKU-I) UCKUN F M.

PATENT INFO: WO 2000000202 A1 20000106 49p
APPLICATION INFO: WO 1999-US14923 19990630
PRIORITY INFO: US 1998-91150 19980630
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-170884 [15]
DESCRIPTION: Chicken beta-actin RT-PCR primer, SEQ ID NO:5.

L9 ANSWER 13 OF 40 DGENE (C) 2003 THOMSON DERWENT
TI New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
AN AAZ87410 DNA DGENE
AB The invention relates to a method of inhibiting **c-jun** proto-oncogene expression in mammalian or avian cells by contacting the cells with a compound that inhibits the activity of Janus family kinase 3 (JAK-3). It also encompasses quinazoline compounds and pharmaceutically acceptable salts thereof, which are capable of selectively inhibiting the activity of JAK-3, but not JAK-1 or JAK-2. JAK kinases play a key role in the JAK/STAT (signal transducers and activators of transcription) signalling pathway. JAK kinases phosphorylate STAT proteins, which in turn causes dimerisation of the STAT proteins. The STAT complexes then translocate to the nucleus where they enhance the transcription of target genes (e.g., **c-jun**). The methods and compounds of the invention may be used to prevent or treat pathological conditions in mammalian or avian cells where **c-jun** **activation** is implicated. Factors which activate **c-jun** include exposure to radiation or to chemical agents that cause DNA damage (e.g., **ara-C**, topoisomerase II inhibitors or alkylating agents). Conditions that may be treated include tissue or organ damage, inflammation, hair loss or the negative effects produced by oxygen free radicals during chemotherapy. The methods and compounds may also be used to treat conditions resulting from the action of internally generated oxygen free radicals, such conditions including ageing and amyelotrophic lateral sclerosis (ALS). Sequences AAZ87407-Z87412 represent PCR primers used in an exemplification of the invention to generate hybridisation probes for use in Northern blot analysis of RNA extracted from irradiated DT-40 chicken lymphoma B-cells. The cells had previously been treated with a JAK-3-specific inhibitor or a general protein tyrosine kinase inhibitor (genistein). Primers AAZ87407-Z87408 were used to amplify a 506 bp JAK-3 probe from chicken genomic DNA. Reverse transcriptase-PCR primer pairs AAZ87409-Z87410 and AAZ87411-Z87412 were used to amplify a 538 bp GAPDH (glyceraldehyde-3-phosphate dehydrogenase) control probe and a 413 bp beta-actin control probe respectively from chicken RNA.
ACCESSION NUMBER: AAZ87410 DNA DGENE
TITLE: New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
INVENTOR: Uckun F M
PATENT ASSIGNEE: (HUGH-N) HUGHES INST.
(UCKU-I) UCKUN F M.
PATENT INFO: WO 2000000202 A1 20000106 49p
APPLICATION INFO: WO 1999-US14923 19990630
PRIORITY INFO: US 1998-91150 19980630
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-170884 [15]
DESCRIPTION: Chicken GAPDH RT-PCR primer, SEQ ID NO:4.

L9 ANSWER 14 OF 40 DGENE (C) 2003 THOMSON DERWENT
TI New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
AN AAZ87409 DNA DGENE
AB The invention relates to a method of inhibiting **c-jun**

proto-oncogene expression in mammalian or avian cells by contacting the cells with a compound that inhibits the activity of Janus family kinase 3 (JAK-3). It also encompasses quinazoline compounds and pharmaceutically acceptable salts thereof, which are capable of selectively inhibiting the activity of JAK-3, but not JAK-1 or JAK-2. JAK kinases play a key role in the JAK/STAT (signal transducers and activators of transcription) signalling pathway. JAK kinases phosphorylate STAT proteins, which in turn causes dimerisation of the STAT proteins. The STAT complexes then translocate to the nucleus where they enhance the transcription of target genes (e.g., **c-jun**). The methods and compounds of the invention may be used to prevent or treat pathological conditions in mammalian or avian cells where **c-jun** **activation** is implicated. Factors which activate **c-jun** include exposure to radiation or to chemical agents that cause DNA damage (e.g., **ara-C**, topoisomerase II inhibitors or alkylating agents). Conditions that may be treated include tissue or organ damage, inflammation, hair loss or the negative effects produced by oxygen free radicals during chemotherapy. The methods and compounds may also be used to treat conditions resulting from the action of internally generated oxygen free radicals, such conditions including ageing and amyelotrophic lateral sclerosis (ALS). Sequences AAZ87407-Z87412 represent PCR primers used in an exemplification of the invention to generate hybridisation probes for use in Northern blot analysis of RNA extracted from irradiated DT-40 chicken lymphoma B-cells. The cells had previously been treated with a JAK-3-specific inhibitor or a general protein tyrosine kinase inhibitor (genistein). Primers AAZ87407-Z87408 were used to amplify a 506 bp JAK-3 probe from chicken genomic DNA. Reverse transcriptase-PCR primer pairs AAZ87409-Z87410 and AAZ87411-Z87412 were used to amplify a 538 bp GAPDH (glyceraldehyde-3-phosphate dehydrogenase) control probe and a 413 bp beta-actin control probe respectively from chicken RNA.

ACCESSION NUMBER: AAZ87409 DNA DGENE
TITLE: New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
INVENTOR: Uckun F M
PATENT ASSIGNEE: (HUGH-N) HUGHES INST.
(UCKU-I) UCKUN F M.
PATENT INFO: WO 2000000202 A1 20000106 49p
APPLICATION INFO: WO 1999-US14923 19990630
PRIORITY INFO: US 1998-91150 19980630
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-170884 [15]
DESCRIPTION: Chicken GAPDH RT-PCR primer, SEQ ID NO:3.

L9 ANSWER 15 OF 40 DGENE (C) 2003 THOMSON DERWENT
TI New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
AN AAZ87408 DNA DGENE
AB The invention relates to a method of inhibiting **c-jun** proto-oncogene expression in mammalian or avian cells by contacting the cells with a compound that inhibits the activity of Janus family kinase 3 (JAK-3). It also encompasses quinazoline compounds and pharmaceutically acceptable salts thereof, which are capable of selectively inhibiting the activity of JAK-3, but not JAK-1 or JAK-2. JAK kinases play a key role in the JAK/STAT (signal transducers and activators of transcription) signalling pathway. JAK kinases phosphorylate STAT proteins, which in turn causes dimerisation of the STAT proteins. The STAT complexes then translocate to the nucleus where they enhance the transcription of target genes (e.g., **c-jun**). The methods and compounds of the invention may be used to prevent or treat pathological conditions in mammalian or avian cells where **c-jun** **activation** is implicated. Factors which activate **c-**

**jun** include exposure to radiation or to chemical agents that cause DNA damage (e.g., **ara-C**, topoisomerase II inhibitors or alkylating agents). Conditions that may be treated include tissue or organ damage, inflammation, hair loss or the negative effects produced by oxygen free radicals during chemotherapy. The methods and compounds may also be used to treat conditions resulting from the action of internally generated oxygen free radicals, such conditions including ageing and amyelotrophic lateral sclerosis (ALS). Sequences AAZ87407-Z87412 represent PCR primers used in an exemplification of the invention to generate hybridisation probes for use in Northern blot analysis of RNA extracted from irradiated DT-40 chicken lymphoma B-cells. The cells had previously been treated with a JAK-3-specific inhibitor or a general protein tyrosine kinase inhibitor (genistein). Primers AAZ87407-Z87408 were used to amplify a 506 bp JAK-3 probe from chicken genomic DNA. Reverse transcriptase-PCR primer pairs AAZ87409-Z87410 and AAZ87411-Z87412 were used to amplify a 538 bp GAPDH (glyceraldehyde-3-phosphate dehydrogenase) control probe and a 413 bp beta-actin control probe respectively from chicken RNA.

ACCESSION NUMBER: AAZ87408 DNA DGENE
TITLE: New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells -
INVENTOR: Uckun F M
PATENT ASSIGNEE: (HUGH-N) HUGHES INST.
(UCKU-I) UCKUN F M.
PATENT INFO: WO 2000000202 A1 20000106 49p
APPLICATION INFO: WO 1999-US14923 19990630
PRIORITY INFO: US 1998-91150 19980630
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-170884 [15]
DESCRIPTION: Chicken **c-jun** PCR primer, SEQ ID NO:2.

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(FILE 'HOME' ENTERED AT 17:48:32 ON 07 MAY 2003)

FILE 'MEDLINE, DGENE, EMBASE, WPIDS, BIOSIS, BIOBUSINESS, JICST-EPLUS, FSTA' ENTERED AT 17:49:25 ON 07 MAY 2003

L1 27419 S C-JUN
L2 4397 S JANUS KINASE
L3 248 S JAK-3
L4 11165 S ARA-C
L5 1457 S TOPOISOMERASE II INHIBITOR
L6 14563 S L1 AND ACTIVATION
L7 91 S L2 AND L3
L8 49 S L7 AND INHIBIT?
L9 40 S L4 AND L6
L10 0 S L9 AND L5
L11 4 S L5 AND L6
L12 0 S L8 AND L9

=> d l8 ti abs ibib 39-49

L8 ANSWER 39 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Human lung myofibroblasts as effectors of the inflammatory process: The common receptor gamma chain is induced by Th2 cytokines, and CD40 ligand is induced by lipopolysaccharide, thrombin and TNF-alpha.
AB The common gamma (gammac) chain, shared by Th1 and Th2 cytokines, is fundamental for the activation of hematopoietic cells, but its role in non-hematopoietic tissues has not been explored. Here we show that in normal lung fibroblasts IL-4 and IL-13 induce the expression of the gammac chain and its association with **Janus kinase** (

**JAK**) **3**, while lung myofibroblasts constitutively express a gammac chain displaying a limited association with JAK3. In the latter cells, without exogenous cytokines, gammac/JAK3 controls, through autocrine loops, tyrosine kinase (TYK) 2 phosphorylation and the balance between functional (IL-4Ralpha, IL-13Ralpha1) and decoy (IL-13Ralpha2) high-affinity receptors. Moreover, JAK3 is also associated with a pre-phosphorylated IL-4Ralpha and CD40. This novel "heterotrimer" (p-IL-4Ralpha, CD40/JAK3) is functional and controls STAT3 phosphorylation and CD40 expression, as shown by use of the specific JAK3 **inhibitor** WHI-P31. In basal culture conditions, CD40 signaling could be induced by the transient establishment of inter-fibroblastic CD40/CD40 ligand (CD40L) functional bridges. Indeed, powerful pro-inflammatory stimuli such as lipopolysaccharide and thrombin can rapidly mobilize CD40L at the surface of lung myofibroblasts. These interactions are modified by IL-13, which triggers the formation of a new type of functional receptor (p-IL-4Ralpha/IL-13Ralpha1/gammac) and also the recruitment and the phosphorylation of JAK3. Treatment with JAK3 **inhibitors** blocks IL-13-induced phosphorylation of JAK2, TYK2 and STAT3, but not of JAK1 and STAT6. These data underline (1) the pivotal role of the gammac chain, CD40/CD40L, JAK3 and IL-13 in the inflammatory-like activation of lung myofibroblasts, (2) the cell-type restraint effects of IL-13 on these cells, and (3) the potential usefulness of JAK3 **inhibitors** in the treatment of asthma.

ACCESSION NUMBER: 2002:529201 BIOSIS
DOCUMENT NUMBER: PREV200200529201
TITLE: Human lung myofibroblasts as effectors of the inflammatory process: The common receptor gamma chain is induced by Th2 cytokines, and CD40 ligand is induced by lipopolysaccharide, thrombin and TNF-alpha.
AUTHOR(S): Doucet, Christelle; Giron-Michel, Julien; Canonica, Giorgio Walter; Azzarone, Bruno (1)
CORPORATE SOURCE: (1) U506 INSERM, Hopital P. Brousse, 16 Av. P.V. Couturier, F-94807, Villejuif: bazzarone@hotmail.com France
SOURCE: European Journal of Immunology, (September, 2002) Vol. 32, No. 9, pp. 2437-2449. http://www.wiley-vch.de/publish/en/journals/alphabeticIndex/2040/?sID=87ce709e9d93384f19ebcbf2d13f6116. print.
ISSN: 0014-2980.
DOCUMENT TYPE: Article
LANGUAGE: English

L8 ANSWER 40 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation.
AB Thymic stromal lymphopoietin (TSLP) is a novel cytokine that was found to promote the development of murine B cells in vitro. Here we describe the cloning and characterization of the human homologue of murine TSLP. This protein, which is expressed in a number of tissues including heart, liver and prostate, prevented apoptosis and stimulated growth of the human acute myeloid leukemia (AML)-derived cell line MUTZ-3. Anti-interleukin (IL)-7 receptor antibodies (Abs) neutralized this effect indicating that TSLP binds to at least part of the IL-7 receptor complex. TSLP induced phosphorylation of signal transducer and activator of transcription (STAT)-5. In contrast to IL-7, TSLP-triggered STAT-5 phosphorylation was not preceded by activation of **janus kinase** (**JAK**) **3**. These findings would be in accordance with the notion, raised previously for the mouse system, that TSLP leads to STAT-5 phosphorylation by activating other kinases than the JAKs. Some other signaling pathways stimulated by many cytokines are not involved in TSLP activity; thus, TSLP did not stimulate activation of ERK1,2 and p70S6K. Furthermore, neutralizing Abs raised against cytokines known to stimulate the growth of MUTZ-3 cells did not **inhibit** the proliferative effects of TSLP, suggesting that TSLP-induced growth was a direct effect. In summary, we describe the cloning of human TSLP and its proliferative

effects on a myeloid cell line. TSLP-induced proliferation is preceded by phosphorylation of STAT-5, but not of **JAK 3**.

ACCESSION NUMBER: 2001:439645 BIOSIS
DOCUMENT NUMBER: PREV200100439645
TITLE: Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation.
AUTHOR(S): Quentmeier, H. (1); Drexler, H. G.; Fleckenstein, D.; Zaborski, M.; Armstrong, A.; Sims, J. E.; Lyman, S. D.
CORPORATE SOURCE: (1) DSMZ, German Collection of Microorganisms and Cell Cultures, Mascheroder Weg 1 B, D-38124, Braunschweig Germany
SOURCE: Leukemia (Basingstoke), (August, 2001) Vol. 15, No. 8, pp. 1286-1292. print.
ISSN: 0887-6924.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 41 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Treatment of allergic asthma by targeting **Janus kinase** 3-dependent leukotriene synthesis in mast cells with 4-(3',5'-dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97.
AB 4-(3',5'-Dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97) is a rationally designed potent **inhibitor** of **Janus kinase** (**JAK**)-**3**. Treatment of mast cells with WHI-P97 **inhibited** the translocation of 5-lipoxygenase (5-LO) from the nucleoplasm to the nuclear membrane and consequently 5-LO-dependent leukotriene (LT) synthesis after IgE receptor/FcepsilonRI crosslinking by >90% at low micromolar concentrations. WHI-P97 did not directly **inhibit** the enzymatic activity of 5-LO, but prevented its translocation to the nuclear membrane without affecting the requisite calcium signal. WHI-P97 was very well tolerated in mice, with no signs of toxicity at dose levels ranging from 5 mug/kg to 50 mg/kg, and LD10 was not reached at a 50 mg/kg dose level when administered as a single i.p. or i.v. bolus dose. Therapeutic WHI-P97 concentrations, which **inhibit** mast cell leukotriene synthesis in vitro, could easily be achieved in vivo after the i.v. or i.p. administration of a single nontoxic 40 mg/kg bolus dose of WHI-P97. Notably, WHI-P97 showed promising biological activity in a mouse model of allergic asthma at nontoxic dose levels. Treatment of ovalbumin-sensitized mice with WHI-P97 prevented the development of airway hyper-responsiveness to methacholine in a dose-dependent fashion. Furthermore, WHI-P97 **inhibited** the eosinophil recruitment to the airway lumen after the ovalbumin challenge in a dose-dependent fashion. Further development of WHI-P97 may therefore provide the basis for new and effective treatment as well as prevention programs for allergic asthma in clinical settings.
ACCESSION NUMBER: 2001:435218 BIOSIS
DOCUMENT NUMBER: PREV200100435218
TITLE: Treatment of allergic asthma by targeting **Janus kinase** 3-dependent leukotriene synthesis in mast cells with 4-(3',5'-dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97.
AUTHOR(S): Malaviya, Ravi; Chen, Chun-Lin; Navara, Christopher; Malaviya, Rama; Liu, Xing-Ping; Keenan, Margaret; Waurzyniak, Barbara; Uckun, Fatih M. (1)
CORPORATE SOURCE: (1) Parker Hughes Institute, 2665 Long Lake Rd., Suite 300, St. Paul, MN, 55113: fatih_uckun@mercury.ih.org USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (December, 2000) Vol. 295, No. 3, pp. 912-926. print.
ISSN: 0022-3565.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 42 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **JAK-3 inhibition** in human T cells abrogates IL-2 production and early T cell clustering: Evidence for an impaired early TCR-signalling.
ACCESSION NUMBER: 2001:396329 BIOSIS
DOCUMENT NUMBER: PREV200100396329
TITLE: **JAK-3 inhibition** in human T cells abrogates IL-2 production and early T cell clustering: Evidence for an impaired early TCR-signalling.
AUTHOR(S): Saeemann, M. D. (1); Boehmig, G. A.; Krieger, P.-M. (1); Diakos, C. (1); Prieschl-Strassmeier, E.; Baumruker, T.; Hoerl, W. H.; Zlabinger, G. (1)
CORPORATE SOURCE: (1) Institute of Immunology, University of Vienna, Vienna Austria
SOURCE: Nephrology Dialysis Transplantation, (June, 2001) Vol. 16, No. 6, pp. A212. print.
Meeting Info.: Annual Congress of the European Renal Association and the European Dialysis and Transplant Association Vienna, Austria June 24-27, 2001
ISSN: 0931-0509.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 43 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Prevention of fatal thromboembolism in mice by selectively targeting **Jak 3** kinase in platelets with 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131.
AB The quinazoline derivative, 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) is a rationally designed specific **inhibitor** of **Janus Kinase** 3. We sought to determine the effects of WHI-P131 on platelet activation and aggregation in vitro as well as bleeding time and thromboplastin-induced fatal thromboembolism in vivo. At low micromolar concentrations, WHI-P131 **inhibited** thrombin-induced signaling events, including degranulation/serotonin release, membrane ruffling, pseudopod formation, and translocation of cytoplasmic proteins to the Tx-soluble and insoluble cytoskeleton. Thrombin-induced tyrosine phosphorylation as well as membrane localization of Stat 1 and Stat3beta were also markedly **inhibited** by WHI-P131. WHI-P131 **inhibited** thrombin-induced (but not collagen-induced) platelet aggregation with an IC50 value of 1.5 muM. **Jak 3** deficient mice also exhibited a decrease in thrombin-induced platelet aggregation, overall tyrosine phosphorylation and phosphorylation of Stat 1 and Stat3beta. WHI-P131 was not toxic to mice when administered systemically at dose levels ranging from 1 mg/kg to 250 mg/kg. Highly effective platelet **inhibitory** plasma concentrations (gtoreq10 muM) of WHI-P131 could be achieved in mice without toxicity. At nontoxic dose levels, WHI-P131 prolonged the tail bleeding time of mice in dose-dependent manner and improved survival in a mouse model of thromboplastin-induced generalized and fatal thromboembolism. The probability of EFS after the thromboplastin challenge was 10+-7% (median survival time=2.5 min) for the vehicle-treated control group (N=20), 30+-15 (median survival time=5.3 min) for warfarin-treated control group (N=20) (P=0.001), and 30+-17% (median survival time =5.2 min) for the WHI-P131-treated test group (25 mg/kg dose level; N=10) (P=0.001) This present study significantly expands our knowledge of the importance of Jak3 and the Stat family proteins in platelets. To our knowledge, WHI-P131 is the first anti-thrombotic agent which prevents platelet aggregation by **inhibiting Jak 3**.
ACCESSION NUMBER: 2001:311605 BIOSIS
DOCUMENT NUMBER: PREV200100311605
TITLE: Prevention of fatal thromboembolism in mice by selectively targeting **Jak 3** kinase in platelets

with 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131.

AUTHOR(S): Tibbles, Heather E. (1); Vassilev, Alexei O. (1); Wendorf, Heather (1); Lorenz, David (1); Zhu, Dan (1); Waurzyniak, Barbara (1); Liu, Xing-Ping (1); Uckun, Fatih M. (1)

CORPORATE SOURCE: (1) Parker Hughes Institute, St. Paul, MN USA

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 273a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L8 ANSWER 44 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI The cytokines ciliary neurotrophic factor and cardiotrophin-1 promote in vitro motoneuron survival through the JAK-STAT signaling pathway.

AB CNTF and Cardiotrophin-1 (CT-1) cytokines that promote cell survival of different neuronal populations. The intracellular signaling pathways that promote neuronal survival remain unknown. Cytokine receptor actiuvation recruits, Janus kinases (JAKs) (JAK1-3 and TYK2) that in turn recruited and tyrosine phosphorylate STATs (STAT1-6), This allows STAT to translocate to the nucleus where it activates transcription of specific genes. Here we show that CNTF and CT-1 promoted the in vitro survival of spinal cord motoneurons. In order to know which intracellular pathway mediates the survival effect of these cytokines we studied the activation of the JAK-STAT, the PI-3 kinase and ERK MAPK pathways. In our model these cytokines induce the tryosine phosphorylation of STAT3 and ERK, but not the activation of the PI 3-kinase pathway. To characterize the involvement of these pathways in the survival effect, we used the JAK3 **inhibitor** I, the PI 3-kinase **inhibitor** LY 294002 and the MEK-**inhibitor** PD 98059. We demonstrate that the JAK3 **inhibitor** I potently suppress CNTF- and CT-1- induced motoneuron survival in a dose-dependent manner. Contrary, neither LY 294002 nor PD 98059 blocked the survival effect. Moreover, we demonstrate that Jak3 **inhibitor** strongly prevents the phosphorylation of its downstream counterpart STAT3 after CNTF or CT-1 stimulation. Taking together these results show that CNTF and CT-1 induce motoneuron survival through the activation of the JAK-STAT pathway, and the PI 3-kinase and the ERK-MAP kinase pathways are not involved in this process.

ACCESSION NUMBER: 2001:108768 BIOSIS

DOCUMENT NUMBER: PREV200100108768

TITLE: The cytokines ciliary neurotrophic factor and cardiotrophin-1 promote in vitro motoneuron survival through the JAK-STAT signaling pathway.

AUTHOR(S): Dolcet, X. (1); Soler, R.; Comella, J. X.

CORPORATE SOURCE: (1) University of Lleida, E-25198 LLEIDA Spain

SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-606.23. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L8 ANSWER 45 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Prevention of development of type 1 diabetes in NOD mice by targeting **Janus kinase (JAK)3** with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131.

ACCESSION NUMBER: 2001:2325 BIOSIS

DOCUMENT NUMBER: PREV200100002325
TITLE: Prevention of development of type 1 diabetes in NOD mice by targeting **Janus kinase** (**JAK**) **3** with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131.
AUTHOR(S): Cetkovic-Cvrlje, Marina (1); Dragt, Angela L. (1); Uckun, Fatih M.
CORPORATE SOURCE: (1) Department of Diabetes and Transplantation, Parker Hughes Institute, Saint Paul, MN USA
SOURCE: Diabetes Research and Clinical Practice, (September, 2000) Vol. 50, No. Suppl. 1, pp. S183. print.
Meeting Info.: 17th International Diabetes Federation Congress on Diabetes Research and Clinical Practice Mexico-City, Mexico November 05-10, 2000
ISSN: 0168-8227.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 46 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI T cell receptor-induced calcineurin activation regulates T helper type 2 cell development by modifying the interleukin 4 receptor signaling complex.
AB The activation of downstream signaling pathways of both T cell receptor (TCR) and interleukin 4 receptor (IL-4R) is essential for T helper type 2 (Th2) cell development, which is central to understanding immune responses against helminthic parasites and in allergic and autoimmune diseases. However, little is known about how these two distinct signaling pathways cooperate with each other to induce Th2 cells. Here, we show that successful Th2 cell development depends on the effectiveness of TCR-induced activation of calcineurin. An **inhibitor** of calcineurin activation, FK506, **inhibited** the in vitro anti-TCR-induced Th2 cell generation in a dose-dependent manner. Furthermore, the development of Th2 cells was significantly impaired in naive T cells from dominant-negative calcineurin Aalpha transgenic mice, whereas that of Th1 cells was less affected. Efficient calcineurin activation in naive T cells upregulated **Janus kinase** ( **Jak**)**3** transcription and the amount of protein. The generation of Th2 cells induced in vitro by anti-TCR stimulation was **inhibited** significantly by the presence of Jak3 antisense oligonucleotides, suggesting that the Jak3 upregulation is an important event for the Th2 cell development. Interestingly, signal transducer and activator of transcription (STAT)5 became physically and functionally associated with the IL-4R in the anti-TCR-activated developing Th2 cells that received efficient calcineurin activation, and also in established cloned Th2 cells. In either cell population, the **inhibition** of STAT5 activation resulted in a diminished IL-4-induced proliferation. Moreover, our results suggest that IL-4-induced STAT5 activation is required for the expansion process of developing Th2 cells. Thus, Th2 cell development is controlled by TCR-mediated activation of the Ca2+/calcineurin pathway, at least in part, by modifying the functional structure of the IL-4R signaling complex.
ACCESSION NUMBER: 2000:325217 BIOSIS
DOCUMENT NUMBER: PREV200000325217
TITLE: T cell receptor-induced calcineurin activation regulates T helper type 2 cell development by modifying the interleukin 4 receptor signaling complex.
AUTHOR(S): Yamashita, Masakatsu; Katsumata, Makoto; Iwashima, Makio; Kimura, Motoko; Shimizu, Chiori; Kamata, Tohru; Shin, Tahiro; Seki, Nobuo; Suzuki, Seiichi; Taniguchi, Masaru; Nakayama, Toshinori (1)
CORPORATE SOURCE: (1) Department of Molecular Immunology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, 260-8670 Japan

SOURCE: Journal of Experimental Medicine, (June 5, 2000) Vol. 191, No. 11, pp. 1869-1879. print.
ISSN: 0022-1007.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 47 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **Inhibition** of thrombin induced platelet aggregation by a specific **inhibitor** of **Janus Kinase** 3 ( **Jak 3**.
ACCESSION NUMBER: 2000:46476 BIOSIS
DOCUMENT NUMBER: PREV200000046476
TITLE: **Inhibition** of thrombin induced platelet aggregation by a specific **inhibitor** of **Janus Kinase** 3 (**Jak 3**
.
AUTHOR(S): Tibbles, H. E. (1); Vassilev, A. O. (1); Liu, X.-P. (1); Uckun, F. M. (1)
CORPORATE SOURCE: (1) Departments of Hematology, Biochemistry, Chemistry, and Drug Discovery Program, Parker Hughes Cancer, Hughes Institute, St. Paul, MN USA
SOURCE: Blood, (Nov. 15 ) Vol. 94, No. 10 SUPPL. 1 PART 2, pp. 67b.
Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 48 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Genetic and biochemical evidence for a critical role of **janus kinase** (**JAK**)-**3** in mast cell-mediated type I hypersensitivity reactions.
AB We investigated the role of JAK3 in IgE receptor/FcepsilonRI-mediated mast cell responses. IgE/antigen induced degranulation and mediator release were substantially reduced with Jak3-/- mast cells from JAK3-null mice that were generated by targeted disruption of Jak3 gene in embryonic stem cells. Further, treatment of mast cells with 3'bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154), a potent **inhibitor** of JAK3, **inhibited** degranulation and proinflammatory mediator release after IgE receptor/FcepsilonRI crosslinking. Thus, JAK3 plays a pivotal role in IgE receptor/FcepsilonRI-mediated mast cell responses and targeting JAK3 may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions.
ACCESSION NUMBER: 1999:249212 BIOSIS
DOCUMENT NUMBER: PREV199900249212
TITLE: Genetic and biochemical evidence for a critical role of **janus kinase** (**JAK**)-**3** in mast cell-mediated type I hypersensitivity reactions.
AUTHOR(S): Malaviya, Ravi; Uckun, Fatih M. (1)
CORPORATE SOURCE: (1) Hughes Institute, 2665 Long Lake Road, Suite 330, Saint Paul, MN, 55113 USA
SOURCE: Biochemical and Biophysical Research Communications, (April 21, 1999) Vol. 257, No. 3, pp. 807-813.
ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 49 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Transcript synthesis and surface expression of the interleukin-2 receptor (alpha-, beta-, and gamma-chain) by normal and malignant myeloid cells.

AB Expression of the interleukin-2 receptor alpha- (IL-2R-alpha), IL-2R-beta-, and the recently identified IL-2R-gamma-chain was examined on a wide range of cells of myeloid origin including neutrophils, monocytes, normal bone marrow-derived myeloid progenitors enriched for CD34+ cells, bone marrow blasts obtained from acute myelogenous leukemia (AML) patients, and permanent myeloid leukemia cell lines by reverse transcriptase-polymerase chain reaction and surface membrane analysis using receptor chain-specific monoclonal antibodies and flow cytometry. Expression of the p75 IL-2R-beta- and the p64 IL-2R-gamma-chain was a common finding in most of the myeloid cell samples investigated, whereas IL-2R-alpha-chain was less frequently expressed. Although the high-affinity IL-2R form (i.e., the alpha+, beta+, gamma+ IL-2R form) was detectable in a small minority of primary AML samples as well as the KG-1 cell line and IL-2 binding to these cells was sufficient to initiate signal transduction as evidenced by an increase in overall protein tyrosine phosphorylation and more specifically in tyrosine phosphorylation of the **Janus kinase** (**JAK**) **3**, in
none of these cell types did exposure to IL-2 affect cell growth kinetics. These results suggest that, in myeloid cells, the IL-2R may not stimulate mitogenic responses or that its components may be expressed in a combinational association with receptors for other cytokines and that IL-2R-gamma may play a regulatory role in normal and malignant myelopoiesis possibly independent from IL-2. Because recent studies by others have indicated that the IL-2R-gamma- chain may be shared by the IL-4R, the IL-7R, and most likely the IL-9R, expression of mRNA of these receptor types was also investigated in these cell samples. Surprisingly, in a substantial part of the myeloid lineage cells examined, an IL-2R-gamma+, IL-4R-, IL-7R- configuration was noted that was, however, frequently associated with expression of IL-9R. Sharing of IL-9R/IL-2R components was furthermore suggested by **inhibition** of 125I-IL-2 binding to primary AML cells with excess of unlabeled IL-9.

ACCESSION NUMBER: 1996:157991 BIOSIS
DOCUMENT NUMBER: PREV199698730126
TITLE: Transcript synthesis and surface expression of the interleukin-2 receptor (alpha-, beta-, and gamma-chain) by normal and malignant myeloid cells.
AUTHOR(S): Schumann, Ralf R.; Nakarai, Takayuki; Gruss, Hans-Juergen; Brach, Marion A.; Von Arnim, Ute; Kirschning, Carsten; Karawajew, Leonid; Ludwig, Wolf-Dieter; Renauld, Jean-Christophe; Ritz, Jerome; Herrmann, Friedhelm (1)
CORPORATE SOURCE: (1) Humboldt Universitaet Berlin, Robert-Roessle Cancer Center, Lindenberger Weg 80, D-13122 Berlin Germany
SOURCE: Blood, (1996) Vol. 87, No. 6, pp. 2419-2427.
ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English

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FILE 'MEDLINE, DGENE, EMBASE, WPIDS, BIOSIS, BIOBUSINESS, JICST-EPLUS, FSTA' ENTERED AT 17:49:25 ON 07 MAY 2003

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L1        27419 S C-JUN
L2         4397 S JANUS KINASE
L3          248 S JAK-3
L4        11165 S ARA-C
L5         1457 S TOPOISOMERASE II INHIBITOR
L6        14563 S L1 AND ACTIVATION
L7           91 S L2 AND L3
L8           49 S L7 AND INHIBIT?
L9           40 S L4 AND L6
L10           0 S L9 AND L5
L11           4 S L5 AND L6
L12           0 S L8 AND L9
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=> d l9 ti abs ibib 30-40

L9 ANSWER 30 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Role of **c-Jun** N-terminal kinase/p38 stress signaling in 1-beta-D-arabinofuranosylcytosine-induced apoptosis.
AB 1-beta-D-Arabinofuranosylcytosine (**ara-C**) induced apoptosis in HL-60 cells, which was preceded by the **activation** of extracellular signal-regulated kinase (ERK), **c-Jun** N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 mitogen-activated protein kinase (MAPK). 2'-Amino-3'-methoxyflavone (PD098059) and 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole (SB203580) were used to inhibit the activity of ERK

and p38, respectively. SEK-AL, a dominant-negative mutant of SEK1, was transfected into HL-60 cells (HL-60/SEK-AL) to assess the role of JNK/SAPK activity in apoptosis. PD098059 (25 muM) inhibited **ara-C** -induced caspase-3-like activity but was ineffective in altering **ara-C**-mediated apoptotic DNA fragmentation and clonogenicity. On the other hand, SB203580 (20 muM) inhibited **ara** -**C**-induced caspase-3-like activity, apoptotic DNA fragmentation, and clonogenicity. The inhibition of JNK1 **activation** in HL-60/SEK-AL cells did not block **ara-C**-induced apoptotic DNA fragmentation. These results suggest that **ara-C**-induced apoptotic DNA fragmentation and loss of clonogenicity occur through a p38-dependent pathway.

ACCESSION NUMBER: 2000:103491 BIOSIS
DOCUMENT NUMBER: PREV200000103491
TITLE: Role of **c-Jun** N-terminal kinase/p38 stress signaling in 1-beta-D-arabinofuranosylcytosine-induced apoptosis.
AUTHOR(S): Stadheim, Terrance A.; Saluta, Gilda R.; Kucera, Gregory L. (1)
CORPORATE SOURCE: (1) Comprehensive Cancer Center, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157 USA
SOURCE: Biochemical Pharmacology, (Feb. 15, 2000) Vol. 59, No. 4, pp. 407-418.
ISSN: 0006-2952.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L9 ANSWER 31 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI The mechanism of **Ara-C**-induced apoptosis of differentiating cerebellar granule neurons.
AB Neurotoxicity is one of the side-effects of the therapeutically useful antitumour agent, **Ara-C** (or 1-beta-D-arabinofuranosyl-cytosine, cytarabine). This agent is also reported to induce cell death of cultured neurons. In this study, we show that **Ara-C** -induced death of differentiating rat cerebellar granule neurons is prevented by cycloheximide at concentrations corresponding to its action in preventing protein synthesis. The death is accompanied by cleavage of the caspase substrate poly ADP ribose polymerase (PARP) and c-Abl-dependent **activation** of the stress-activated protein kinases **c-Jun** N-terminal kinase and p38. However, **c-Jun** levels do not rise and the **activation** of the stress-activated protein kinases is not required for this form of neuronal death. Cyclin-dependent kinase (cdk) activity and inappropriate cell-cycle re-entry have been implicated in some forms of death in differentiated neurons. Here we show that **Ara-C** -induced death of cerebellar granule neurons is prevented by an inhibitor of cdk4, whereas inhibition of cdk1, -2 and -5 mimics the death, and non-cdk4/6 cdks are inhibited by **Ara-C** treatment. Cdk1 and -2 are dramatically down-regulated during neuronal differentiation, and neither **Ara-C** nor inhibition of these cdks induces death in mature neurons. This mechanism could also play a significant role in the neurotoxicity associated with the therapeutic use of **Ara-C**, as cdk levels can be upregulated in stressed neurons of adult brain. We propose that the balance between cdk4/6 and cdk1/2/5 activity may determine the survival of early differentiating neurons, and that DNA-damaging agents may induce neuronal death by inhibiting cdk1/2/5 under conditions which require these activities for survival.

ACCESSION NUMBER: 1999:195601 BIOSIS
DOCUMENT NUMBER: PREV199900195601
TITLE: The mechanism of **Ara-C**-induced apoptosis of differentiating cerebellar granule neurons.
AUTHOR(S): Courtney, Michael J. (1); Coffey, Eleanor T.

CORPORATE SOURCE: (1) Centre for Mechanisms of Human Toxicity, University of Leicester, Hodgkin Building, Leicester, LE1 9HN UK
SOURCE: European Journal of Neuroscience, (March, 1999) Vol. 11, No. 3, pp. 1073-1084.
ISSN: 0953-816X.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 32 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Effects of **Ara-C** on neutral sphingomyelinase and mitogen- and stress-activated protein kinases in T-lymphocyte cell lines.
AB Neutral sphingomyelinase (SMase) can be activated by extracellular signals to produce ceramide, which may affect mitogen-activated protein kinase (MAPK) activities. Neutral SMase activity was assessed in membranes from Jurkat, a human T-cell line, and EL4, a murine T-cell line. **Ara-C** activated SMase within 10 minutes in both Jurkat and EIA cells, while phorbol ester (PMA) had no effect. PMA, but not **Ara-C** or ceramides, activated ERK MAPKs in Jurkat and EL4. PMA acted synergistically with ionomycin to activate JNK MAPKs in Jurkat and EL4 within 10 minutes. **Ara-C** activated JNKs only after prolonged incubation (90-120 minutes). Thus, ceramide is not a positive signal for ERK **activation** in T-cell lines. The effects of **Ara-C** on JNK activity may be mediated through secondary response pathways.
ACCESSION NUMBER: 1997:17994 BIOSIS
DOCUMENT NUMBER: PREV199799317197
TITLE: Effects of **Ara-C** on neutral sphingomyelinase and mitogen- and stress-activated protein kinases in T-lymphocyte cell lines.
AUTHOR(S): Bradshaw, Cynthia D.; Ella, Krishna M.; Thomas, Aydrian L.; Qi, Chen; Meier, Kathryn E. (1)
CORPORATE SOURCE: (1) Dep. Cell Mol. Pharmacol. Exp. Therapeutics, Med. Univ. S.C., 171 Ashley Ave., Charleston, SC 29425 USA
SOURCE: Biochemistry and Molecular Biology International, (1996) Vol. 40, No. 4, pp. 709-719.
ISSN: 1039-9712.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 33 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Bryostatin 1 potentiates 1-(beta-D-arabinofuranosyl)cytosine-mediated antiproliferative effects in **c-jun** dominant-negative human myeloid leukemia cells (U937/TAM67) through a nonapoptotic mechanism.
AB Recent studies suggest that exposure of leukemic cells to a differentiating stimulus following a DNA-damaging agent leads to potentiation of apoptosis or programmed cell death. The present studies were undertaken to evaluate the contribution of the transcription factor **c-Jun** to apoptosis and growth inhibition induced by the sequential administration of 1-beta-D-arabinofuranosylcytosine ( **ara-C**) and the protein kinase C activator bryostatin 1 in human monocytic leukemia cells (U937). To address this issue, a U937 cell line stably transfected with a dominant-negative, **c-Jun** transactivation domain-deficient mutant (TAM67), was employed. The mutant TAM67 protein interferes with normal **c-Jun** function and AP-1 **activation** through a "quenching" mechanism. TAM67-expressing cells and cells containing empty vector (pMM) were equally susceptible to apoptosis induced by exposure to **ara-C** (1 mu-M; 6 h); moreover, this effect was not altered by subsequent exposure of cells to bryostatin 1 (10 nM; 24 h). However, clonogenic TAM67-expressing cells were less susceptible to the antiproliferative effects of **ara-C** and more susceptible to growth inhibition by bryostatin 1 than their empty vector counterparts. In addition, subsequent exposure to bryostatin 1

substantially increased growth inhibition by **ara-C** in TAM67-expressing cells despite failing to potentiate apoptosis. Whereas 10 nM bryostatin 1 was ineffective in triggering maturation of pMM cells, it partially induced differentiation in their TAM67-expressing counterparts, manifested by increased expression of the maturation marker CD11b, modest up-regulation of native **c-Jun**, and limited dephosphorylation of the retinoblastoma protein pRb. Sequential administration of **ara-C** followed by bryostatin 1 led to further up-regulation of native **c-Jun**. particularly in TAM67-expressing cells, but failed to induce pRb hypophosphorylation in either cell line. Collectively, these findings indicate that bryostatin 1 reverses, at least in part, the reduced susceptibility of clonogenic U937 cells to **ara-C** conferred by **c-Jun** dysregulation, and further suggest that this phenomenon proceeds via nonapoptotic mechanisms.

ACCESSION NUMBER: 1996:527206 BIOSIS
DOCUMENT NUMBER: PREV199699249562
TITLE: Bryostatin 1 potentiates 1-(beta-D-arabinofuranosyl)cytosine-mediated antiproliferative effects in **c-jun** dominant-negative human myeloid leukemia cells (U937/TAM67) through a nonapoptotic mechanism.
AUTHOR(S): Freemerman, Alex J.; Maloney, Nancy J.; Birrer, Michael J.; Szabo, Eva; Grant, Steven (1)
CORPORATE SOURCE: (1) Dep. Med., Div. Hematol./Oncol., MCV Stn. Box 230, Medical Coll. Virginia, Richmond, VA 23298-0230 USA
SOURCE: Molecular and Cellular Differentiation, (1996) Vol. 4, No. 3, pp. 247-262.
ISSN: 1065-3074.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 34 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI C-Abl **activation** regulates induction of the SEK1/stress-activated protein kinase pathway in the cellular response to 1-beta-D-arabinofuranosylcytosine.
AB Previous work has shown that treatment of cells with the antimetabolite 1-beta-D-arabinofuranosylcytosine (**ara-C**) is associated with induction of the **c-jun** gene. The present studies demonstrate that **ara-C** activates the c-Abl non-receptor tyrosine kinase. We also demonstrate that activity of the stress-activated protein kinase (SAP kinase/JNK) is increased in **ara-C**-treated cells. Using cells deficient in c-Abl (Abl-/-) and after introduction of the c-abl gene, we show that **ara-C**-induced c-Abl activity is necessary for the stimulation of SAP kinase. Other studies using cells transfected with a SEK1 dominant negative demonstrate that **ara-C**-induced SAP kinase activity is SEK1-dependent. Furthermore, we show that overexpression of truncated c-Abl results in **activation** of the SEK1/SAP kinase cascade.

ACCESSION NUMBER: 1996:60039 BIOSIS
DOCUMENT NUMBER: PREV199698632174
TITLE: C-Abl **activation** regulates induction of the SEK1/stress-activated protein kinase pathway in the cellular response to 1-beta-D-arabinofuranosylcytosine.
AUTHOR(S): Kharbanda, Surender (1); Pandey, Pramod; Ren, Ruibao; Mayer, Bruce; Zon, Leonard; Kufe, Donald
CORPORATE SOURCE: (1) Div. Cancer Pharmacol., Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115 USA
SOURCE: Journal of Biological Chemistry, (1995) Vol. 270, No. 51, pp. 30278-30281.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 35 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Involvement of stress-activated protein kinase in the cellular response to 1-beta-D-arabinofuranosylcytosine and other DNA-damaging agents.
AB The cellular response to 1-beta-D-arabinofuranosylcytosine (**ara-C**) includes **activation** of Jun/AP-1, induction of **c-jun** transcription, and programmed cell death. The stress-activated protein (SAP) kinases stimulate the transactivation function of **c-Jun** by amino terminal phosphorylation. The present work demonstrates that **ara-C** activates p54 SAP kinase. The finding that SAP kinase is also activated by alkylating agents (mitomycin C and cisplatinum) and the topoisomerase I inhibitor 9-amino-camptothecin supports DNA damage as an initial signal in this cascade. The results demonstrate that **ara-C** also induces binding of SAP kinase to the SH2/SH3-containing adapter protein Grb2. SAP kinase binds to the SH3 domains of Grb2, while interaction of the p85 alpha-subunit of phosphatidylinositol 3-kinase (PI 3-kinase) with the Grb2 SH2 domain results in the formation of a SAP kinase/Grb2/PI 3-kinase complex. The results also demonstrate that **ara-C** treatment is associated with inhibition of lipid and serine kinase activities of PI 3-kinase. The potential significance of the **ara-C**-induced interaction between SAP kinase and PI 3-kinase is further supported by the demonstration that Wortmannin, an inhibitor of PI 3-kinase, stimulates SAP kinase activity. The finding that Wortmannin treatment is also associated with internucleosomal DNA fragmentation may support a potential link between PI 3-kinase and regulation of both SAP kinase and programmed cell death.
ACCESSION NUMBER: 1996:35653 BIOSIS
DOCUMENT NUMBER: PREV199698607788
TITLE: Involvement of stress-activated protein kinase in the cellular response to 1-beta-D-arabinofuranosylcytosine and other DNA-damaging agents.
AUTHOR(S): Saleem, Ahamed; Datta, Rakesh; Yuan, Zhi-Min; Kharbanda, Surender; Kufe, Donald (1)
CORPORATE SOURCE: (1) Div. Cancer Pharmacol., Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115 USA
SOURCE: Cell Growth & Differentiation, (1995) Vol. 6, No. 12, pp. 1651-1658.
ISSN: 1044-9523.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 36 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Augmentation by aphidicolin of 1-beta-D-arabinofuranosylcytosine-induced **c-jun** and NF-kappa-B **activation** in a human myeloid leukemia cell line: Correlation with apoptosis.
AB 1-beta-D-arabinofuranosylcytosine (**ara-C**) (2 mu-M) can induce apoptosis in a human myeloid leukemia cell line, U937, after 4 h of incubation. Pretreatment of cells with aphidicolin (2 mu-M) augments **ara-C**-induced apoptosis, since it was first observed at 0.4 mu-M **ara-C** and became more intense at 2 and 10 mu-M. Although aphidicolin itself had a marginal effect on **c-jun** expression, it significantly augmented **ara-C** induced **c-jun** upregulation by shortening the lag time and lowering **ara-C** concentrations necessary for the induction of detectable **c-jun** transcripts. Aphidicolin and **ara-C** acted synergistically to increase NF-kappa-B DNA binding activity as determined by an electrophoretic mobility shift assay. Expression of c-myc was slightly increased through the DNA degradative phase, and was then downregulated. Thus, the **activation** of NF-kappa-B and **c-jun** expression seems to be well correlated with the potentiation by aphidicolin of **ara-C**-induced apoptosis.
ACCESSION NUMBER: 1995:536684 BIOSIS

DOCUMENT NUMBER: PREV199598550984
TITLE: Augmentation by aphidicolin of 1-beta-D-arabinofuranosylcytosine-induced **c-jun** and NF-kappa-B **activation** in a human myeloid leukemia cell line: Correlation with apoptosis.
AUTHOR(S): Kuwakado, Katsuji; Kubota, Masaru (1); Bessho, Rikimaru; Kataoka, Akihiro; Usami, Ikuya; Lin, Ying Wei; Okuda, Akiro; Wakazono, Yoshihiro
CORPORATE SOURCE: (1) 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606 Japan
SOURCE: Leukemia Research, (1995) Vol. 19, No. 9, pp. 645-650. ISSN: 0145-2126.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 37 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI 1-beta-D-Arabinofuranosylcytosine activates serine/threonine protein kinases and **c-jun** gene expression in phorbol ester-resistant myeloid leukemia cells.
AB 1-beta-D-Arabinofuranosylcytosine (**ara-C**) is an effective antileukemic agent that misincorporates into DNA. Recent studies have demonstrated that **ara-C** treatment is associated with transient induction of the **c-jun** early response gene. The present studies have examined the effects of **ara-C** on **c-jun** expression in a phorbol ester-resistant variant of the HL-60 myeloid leukemia cell line, designated HL-525, that is deficient in protein kinase C (PKC)-mediated signal transduction and fails to respond to 12-O-tetradecanoylphorbol-13-acetate with induction of **c-jun** transcripts. The results demonstrate that treatment of HL-525 cells with **ara-C** is associated with transcriptional **activation** of the **c-jun** gene. We also demonstrate that **ara-C** treatment is associated with **activation** of a PKC-like activity. Partial purification of this Ca-2+-independent activity has demonstrated phosphorylation of synthetic peptides derived from (a) amino acids 4-14 of myelin basic protein and (b) the pseudosubstrate region of PKC (amino acids 19-31), with substitution of Ala-25 with serine. The finding that the **ara-C**-induced activity is inhibited by the pseudosubstrate PKC(19-36) supports the **activation** of a PKC-like enzyme. Because PKC can act upstream of the mitogen-activated protein (MAP) kinases, we studied the effects of **ara-C** treatment on MAP kinase activity. The results demonstrate that MAP kinase is activated in **ara-C**-treated cells and that the kinetics of this **activation** are similar to those of the PKC-like activity. Because 12-O-tetradecanoylphorbol-13-acetate has little, if any, effect on the PKC-like and MAP kinase activities in HL-525 cells, these findings suggest that **ara-C** activates a distinct signaling cascade that may contribute to induction of the **c-jun** gene.
ACCESSION NUMBER: 1994:502189 BIOSIS
DOCUMENT NUMBER: PREV199497515189
TITLE: 1-beta-D-Arabinofuranosylcytosine activates serine/threonine protein kinases and **c-jun** gene expression in phorbol ester-resistant myeloid leukemia cells.
AUTHOR(S): Kharbanda, Surender; Emoto, Yutaka; Kisaki, Hiroshi; Saleem, Ahamed; Kufe, Donald (1)
CORPORATE SOURCE: (1) Dana-Farber Cancer Inst., 44 Binney St., Boston, MA 02115 USA
SOURCE: Molecular Pharmacology, (1994) Vol. 46, No. 1, pp. 67-72. ISSN: 0026-895X.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 38 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **Activation** of the jun-D gene during treatment of human myeloid leukemia cells with 1-beta-D-arabinofuranosylcytosine.

AB The jun-D gene is a member of the **c-jun** family of early response genes that code for DNA binding proteins. The present studies demonstrate that 1-beta-D-arabinofuranosylcytosine (**ara-C**) increases jun-D expression in HL-525 myeloid leukemia cells. This induction by **ara-C** was maximal at 6 hr and transient. In contrast, **ara-C** had no detectable effect on the gene coding for the cAMP-responsive element binding protein 1. Nuclear run-on assays demonstrated that **ara-C** treatment is associated with an increased rate of jun-D transcription. The results also show that jun-D transcripts are stabilized at a posttranscriptional level in **ara-C**-treated cells. Taken together, these results demonstrate that **ara-C** induces expression of the jun-D gene and that this effect is regulated by transcriptional and posttranscriptional mechanisms.

ACCESSION NUMBER: 1993:435214 BIOSIS
DOCUMENT NUMBER: PREV199396089839
TITLE: **Activation** of the jun-D gene during treatment of human myeloid leukemia cells with 1-beta-D-arabinofuranosylcytosine.
AUTHOR(S): Kharbanda, Surender; Huberman, Eliezer; Kufe, Donald (1)
CORPORATE SOURCE: (1) Lab. Clin. Pharmacol., Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115 USA
SOURCE: Biochemical Pharmacology, (1993) Vol. 45, No. 10, pp. 2055-2061.
ISSN: 0006-2952.
DOCUMENT TYPE: Article
LANGUAGE: English

L9 ANSWER 39 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **ACTIVATION** OF THE AP-1 TRANSCRIPTION FACTOR BY ARABINOFURANOSYLCYTOSINE IN MYELOID LEUKEMIA CELLS.

AB Previous studies have shown that 1-.beta.-D-arabinofuranosylcytosine (**ara-C**) induces transcription of the **c-jun** immediate early response gene in human myeloid leukemia cells. The present work has examined the mechanisms responsible for this effect. Deleted forms of the **c-jun** promoter were linked to the chloramphenicol acetyltransferase (CAT) gene and transfected into KG-1 cells. The results demonstrate that **ara-C**-induced **c-jun** transcription is mediated by an element between positions -74 and -20 upstream to the start site. Electrophoretic mobility shift assays with the fragment f(-74/-20) showed an increase in binding with nuclear proteins from **ara-C**-treated cells as compared with untreated cells. Competition with an oligonucleotide containing the AP-1 consensus sequence indicated that **ara-C** stimulates binding of nuclear proteins at the AP-1 site in the **c-jun** promoter. These findings were confirmed in other gel shift studies with the collagenase enhancer AP-1 consensus sequence and with a DNA fragment containing an altered AP-1 site. The binding of JUN/AP-1 was maximal at 1 hour of **ara-C** treatment and decreased to baseline levels at 12 hours. The finding that **ara-C** induces AP-1 binding in the absence of protein synthesis indicated that this agent activities already synthesized JUN/AP-1. To confirm these findings, the AP-1 consensus sequence was introduced 5' to the heterologous SV40 promoter. The results show that AP-1 enhances SV40 promoter activity in **ara-C**-treated cells. Taken together, these findings indicate that: (1) enhancement of JUN/AP-1 activity in **ara-C**-treated cells involves a posttransitonal modification of JUN/AP-1; and (2) binding of activated JUN/AP-1 to the AP-1 site in the **c-jun** promoter confers **ara-C** inducibility of this gene.

ACCESSION NUMBER: 1992:168203 BIOSIS
DOCUMENT NUMBER: BA93:90528

TITLE: **ACTIVATION** OF THE AP-1 TRANSCRIPTION FACTOR BY ARABINOFURANOSYLCYTOSINE IN MYELOID LEUKEMIA CELLS.
AUTHOR(S): BRACH M A; HERRMANN F; KUFE D W
CORPORATE SOURCE: DANA-FARBER CANCER INST., 44 BINNEY STREET, BOSTON, MASS. 02115.
SOURCE: BLOOD, (1992) 79 (3), 728-734.
CODEN: BLOOAW. ISSN: 0006-4971.
FILE SEGMENT: BA; OLD
LANGUAGE: English

L9 ANSWER 40 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI REGULATION OF **C-JUN** GENE EXPRESSION IN HL-60 LEUKEMIA CELLS BY 1-BETA-D ARABINOFURANOSYLCYTOSINE POTENTIAL INVOLVEMENT OF A PROTEIN KINASE C DEPENDENT MECHANISM.
AB 1-.beta.-D-Arabinofuranosylcytosine (**ara-C**) is an effective chemotherapeutic agent that incorporates into DNA and results in DNA fragmentation. Recent work has demonstrated that **ara-C** transiently induces expression of the **c-jun** immediate early response gene. The present studies in HL-60 myeloid leukemia cells extend these findings by demonstrating that the increase in **c-jun** mRNA levels at 6 h of **ara-C** treatment is regulated by a transcriptional mechanism. In contrast, the subsequent down-regulation of **c-jun** expression is controlled by a posttranscriptional decrease in the stability of the **c-jun** transcripts. Previous work in phorbol ester treated cells has indicated that **c-jun** expression is regulated by the **activation** of protein kinase C. The present results demonstrate that protein kinase C activity is increased in **ara-C**-treated cells. This increase was maximal at 60 min and remained detectable through 6 h of **ara-C** exposure. Moreover, the induction of **c-jun** transcripts by **ara-C** was inhibited by the isoquinolinesulfonamide derivative H7, but not by HA1004, suggesting that this effect is mediated by protein kinase C. **Ara-C**-induced **c-jun** expression was also inhibited by staurosporine, another inhibitor of protein kinase C. Taken together, these results indicate that the cellular response to **ara-C** includes the **activation** of protein kinase C and that **ara-C** potentially induces **c-jun** transcription by a protein kinase C dependent signaling mechanism.
ACCESSION NUMBER: 1991:457352 BIOSIS
DOCUMENT NUMBER: BA92:102132
TITLE: REGULATION OF **C-JUN** GENE EXPRESSION IN HL-60 LEUKEMIA CELLS BY 1-BETA-D ARABINOFURANOSYLCYTOSINE POTENTIAL INVOLVEMENT OF A PROTEIN KINASE C DEPENDENT MECHANISM.
AUTHOR(S): KHARBANDA S; DATTA R; KUFE D
CORPORATE SOURCE: LABORATORY CLINICAL PHARMACOLOGY, DANA-FARBER CANCER INSTITUTE, HARVARD MEDICAL SCHOOL, BOSTON, MASS. 02115.
SOURCE: BIOCHEMISTRY, (1991) 30 (32), 7947-7952.
CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: English